Predictors of recovery after cholecystectomy

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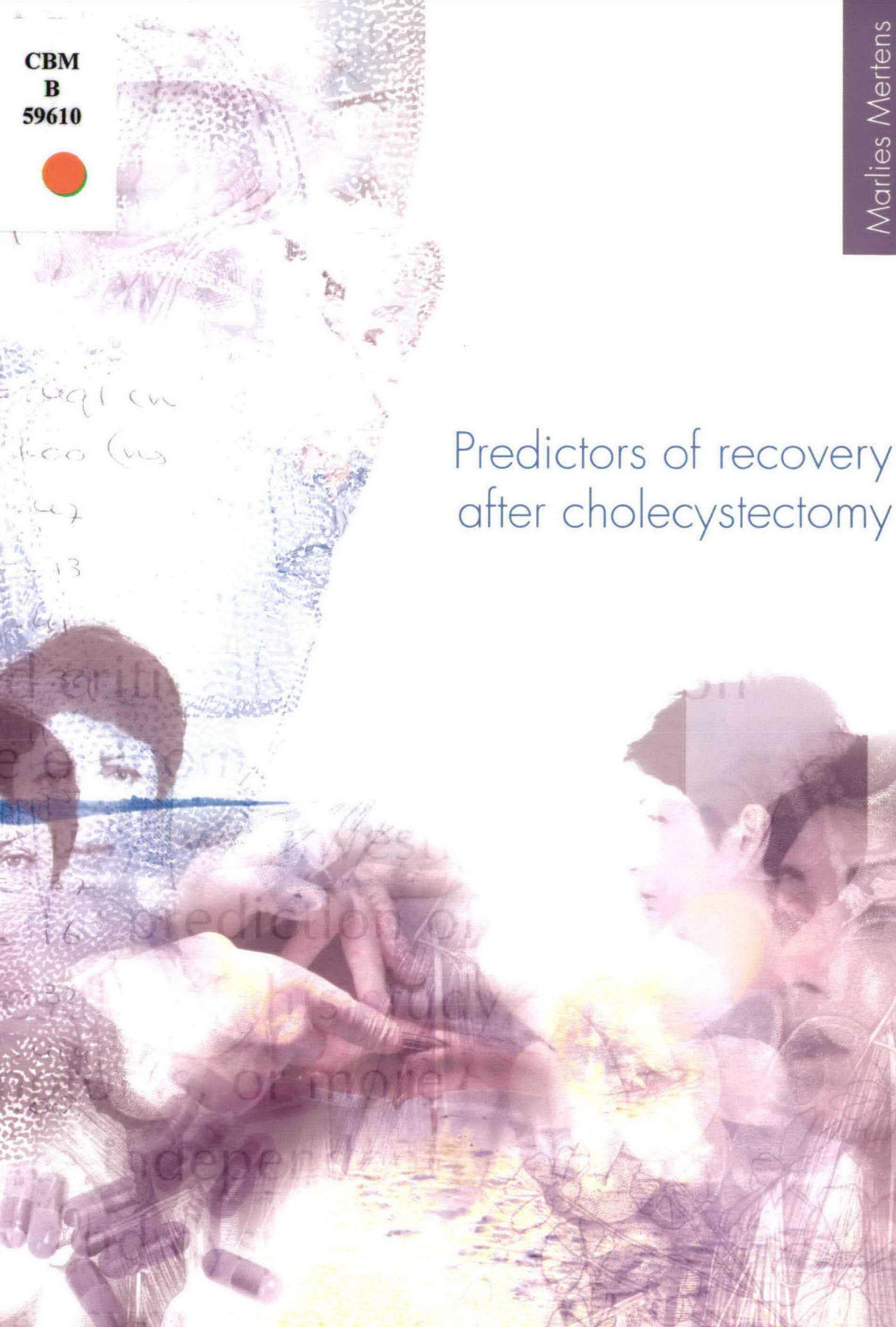

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Chapter 1

Introduction and outline of the thesis

Introduction

Gallstone disease

Gallstone disease (cholelithiasis) is a common condition that affects 5% – 22% of the people in Western countries[1-3] and in the Netherlands more than 30,000 patients are diagnosed with gallstone disease yearly[4]. Traditionally, patients with cholelithiasis are characterised as 'fat fertile females in their forties', however this picture deserves some differentiation. Generally, cholelithiasis is more prevalent in women than in men (10.5% – 11.5% vs. 6.5% – 7.8%)[2, 5, 6]. The male-female ratio ranges from 1:4 during reproductive years to equality in older patients. The overall prevalence of cholelithiasis also increases with age[2, 7]. Furthermore, cholelithiasis has a higher prevalence among native populations in North and South America[8]. Besides age and sex, hormonal influences and ethnicity, dyspeptic symptoms, high body mass index (BMI), use of tobacco, alcohol consumption, and use of hypolipidemic drugs are risk factors for cholelithiasis[5].

Diagnosis

Although the majority of patients suffer from silent gallstones or asymptomatic cholelithiasis[3], 10% – 30% of the patients report clinical symptoms[9-15]. Biliary pain, which has been defined as 'a severe steady pain, lasting more than 15 – 30 minutes, usually located in the epigastrium and/or right upper quadrant, and sometimes radiating to the back' [7] is the most distinguishing symptom of symptomatic cholelithiasis. Biliary colic, pain radiating to the back, and a positive reaction to standard analgesics were only with limited significance related to the presence of gallstones[16, 17]. Symptoms such as upper abdominal pain, nausea, and vomiting are related to the presence of gallstones[18], whereas classical dyspeptic symptoms, such as flatulence, heartburn, acid regurgitation, bloating, and belching are not. As the clinical symptomatology of this condition gives insufficient support for a correct diagnosis, additional ultrasound investigation is recommended for diagnosing cholelithiasis[19].

Treatment

Cholecystectomy is the golden standard in symptomatic cholelithiasis. Essentially, elective cholecystectomy is a prophylactic treatment which prevents recurrent symptoms and complications. Since the introduction in 1985, laparoscopic

cholecystectomy is preferred over preceding techniques and the age standardised cholecystectomy rate has increased with 20%[20]. However, the risks of cholecystectomy are generally underestimated and cholecystectomy still entails the risk of mortality (0% – 0.2%), complications (5.0%), and bile duct injuries (0.2% – 1.0%)[21, 22]. In case of conservative management, only 31% of the patients report recurrence of biliary pain within a year[23] and the risk of complications such as acute cholecystitis, acute pancreatitis, or biliary duct obstruction is small (1% – 2% per year)[24, 25]. Therefore, conservative treatment or 'wait and see', may be a safe alternative for elective cholecystectomy. The latter treatment option however is seldomly chosen by gastroenterologists and surgeons.

Symptomatic outcome after cholecystectomy

The majority of patients reported positive outcomes after cholecystectomy, such as a relief of symptoms (46% – 67%), more specifically upper abdominal pain and dyspeptic symptoms (72% and 56%, respectively)[26].

At six months postoperatively, it was found that 13% of the patients reported persistent pain[14]. Colicky abdominal pain and back pain were relieved, whereas nagging abdominal pain did not improve in the course of six months[27]. A shift from predominantly biliary symptoms preoperatively, to predominantly dyspeptic symptoms at six months was observed[12]. Nausea and vomiting improved, whereas flatulence and fat intolerance did not[27]. Moreover, 3% – 18% of the patients developed diarrhoea[14, 27]. Preoperative bloating, constipation, and previous or current use of psychotropic medication were associated with poor outcome at six months after cholecystectomy[14].

At one year after cholecystectomy, a comparable pattern was found and 18% – 31% of the patients reported persistence of pain[28-30]. One year postoperatively, it was demonstrated that biliary symptoms had improved, whereas symptoms of reflux, irritable bowel syndrome, and chronic pain did not improve[30]. In addition, 30% – 40.4% of the patients did not report improvement of gastrointestinal symptoms[31, 32] and 10% reported persistence of digestive symptoms[32]. Flatulence and dyspepsia was reported by 19% and 24% of the patients respectively[33]. In contrast to findings of negative symptomatic outcome, 95% of the patients rated the success of the procedure as fair to excellent[33]. Higher preoperative psychological symptoms, neuroticism, and introversion were associated with a lack of improvement[28, 29, 31]. Preoperative dyspeptic symptoms,

preoperative pain characteristics, and symptoms coinciding with pain were associated with postoperative pain at one year[28, 29].

Long term follow-ups (one to three years) showed that abdominal complaints persisted in 30.5% of the patients[34]. More specifically, 6.4% of the patients reported persistent biliary colics and 45.3% reported persistent flatulence. In contrast, only 3.2% of the patients were dissatisfied with the results of cholecystectomy. At ten years after cholecystectomy, 18.5% of the patients reported persistent symptoms[35]. Furthermore, at ten years after the procedure, patients with typical biliary symptoms showed more improvement than patients with atypical symptoms[35].

In summary, after cholecystectomy, approximately one third of all patients report persisting symptoms on long term follow-up. On the long run patients with typical biliary symptoms report more improvements than patients with atypical symptoms or dyspeptic symptoms. Flatulence and diarrhoea are often experienced symptoms after cholecystectomy. Atypical symptoms, usually of dyspeptic nature, and psychological factors tend to be related to negative symptomatic outcome after cholecystectomy.

Quality of life

Traditionally, outcome assessment has focussed on classical or mechanistic end-points of recovery, such as survival, complications, and symptomatic relief, which represent the perspective of medical doctors. In the last decades the patients' perspective has won ground and hermeneutic endpoints of recovery, such as quality of life (QoL), autonomy, and duration of absence from work, have increasingly been recognised as relevant outcome measures of therapies and procedures. So far, outcome assessment after cholecystectomy has primarily focussed on mechanistic endpoints[36], and subjective endpoints are scarcely investigated.

Subjective endpoints, such as health status, health related quality of life (HRQoL), and QoL, are multidimensional concepts incorporating physical, psychological, and social aspects[37]. These concepts have in common that the definition of health of the World Health Organization (WHO) - 'A state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity' – was taken to formulate the three core domains. There is also a difference between these concepts. Health status refers to patients' physical, psychological and social functioning, which is not related to the individual patient' perception, values, and expectations[37]. The WHO defined QoL as 'an individual's perception of his/her position in life in the context of the culture and value

system in which he/she lives and in relation to his/her goals, expectations, and standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment'[38]. Thus, apart from incorporating the patients' functioning, QoL also focuses on patients' evaluation of that functioning. As health status and QoL are related, but different concepts, these terms can not be used interchangeably[39-41]. Furthermore, health-related QoL covers only the physical, psychological, and social domains, whereas QoL covers more than the three domains mentioned in the definition of health of the WHO (e.g. environment). In fact, QoL is a container concept that incorporates *and* goes beyond health status and health-related QoL.

While previous studies assessed subjective outcomes of recovery after cholecystectomy, QoL according to the definition of the WHO, has not been investigated so far. The majority of studies assessed health status[30, 33, 42-47] and few studies used self-constructed ratings of patient satisfaction[12, 33, 48]. One study indicated that in the course of one year after cholecystectomy health status improved[30] and was comparable to health status in the general population, with exception to breathing and sleeping[49]. However, another study demonstrated that five years after diagnosis, improvements of health status were observed in patients with cholelithiasis, regardless of cholecystectomy[46]. Improved health status at one year was predicted by low surgical risks[44]. Furthermore, a clinical presentation of typical biliary symptoms predicted higher patient satisfaction at three months after cholecystectomy[48].

Personality traits

People differ in the way they perceive situations, how they feel under certain conditions, and how they react to other people. Stable personality traits are characteristics that describe differences between people with regard to enduring patterns of feelings, thoughts and behaviour[50]. In fact, individuals' cognitive styles, motivational and affective tendencies are found to be stable over time[51, 52]. Trait Anxiety (TA) refers to relatively stable individual differences in anxiety proneness, i.e. differences between people in the tendency to respond to situations perceived as threatening with heightened anxiety intensity[53]. TA can be understood as an underlying disposition that remains latent unless it is activated by certain stimuli in the environment[54]. Measured with the Spielberger State Trait Anxiety Inventory (STAI) trait-scale, TA encompasses feelings of anxiety and

depression and generally refers to negative affect[55]. Several studies investigated the impact of TA on early post-cholecystectomy recovery[56-59] and demonstrated that TA predicted early postoperative pain[56, 57], emotional and physical well-being[56], and the use of narcotics[57]. In contrast, two studies found that TA was not associated with early postoperative pain and hospital stay[58, 59]. Evidence of the impact of TA is inconclusive and reserach has been limited to short-term postoperative recovery.

Aim and design of the study

In symptomatic cholelithiasis, cholecystectomy is the preferred treatment over conservative treatment. Cholecystectomy is an elective procedure performed to improve the patient's QoL and to prevent complications. However, a substantial group of patients reports persisting symptoms after cholecystectomy. On the other hand, the risk of complications related to conservative treatment is small and is usually overestimated. Therefore, appropriateness of cholecystectomy may be a matter of debate, especially in patients who are at risk for negative outcomes. Preoperative recognition of these patients is essential to improve management of cholelithiasis and to prevent unsuccessful cholecystectomies.

The aim of the present study is to identify risk factors for negative symptomatic outcomes and low QoL among clinical symptoms and psychological variables. We expected long term outcomes (> 6 weeks) to be most informative with regard to clinical decision making. Potential predictors were investigated at different time points, namely six weeks, six months, and one year after cholecystectomy.

The results of this prospective follow-up study are described in this thesis. Patients were recruited from the Department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Consecutive patients (18 – 65 years) with diagnosed symptomatic cholelithiasis, awaiting an elective laparoscopic cholecystectomy were eligible for the study. Patients undergoing an emergency procedure or intended open cholecystectomy were not included. Furthermore, patients in the American Society of Anaesthesiologists (ASA) class III or IV, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), psychiatric diseases, and insufficient knowledge of the Dutch language were excluded from the study.

Medical information

All patients underwent cholecystectomy following a standard surgical procedure. Open introduction was performed in all patients regardless of previous abdominal surgery. Pneumoperitoneum was created using the subumbilical trocar with an intra-abdominal pressure up to 12 mmHg. Three trocars for instruments were inserted. The dissection of the cystic artery and cystic duct, identifying Calot's triangle, was performed using a three points 'flag' technique. The cystic duct and artery were clipped and transsected. After complete dissection of the gallbladder, it was removed either through the subumbilical or subxyphoidal trocar. Fascia defects as a result of the insertion of the 10mm trocar and the open introduction of the subumbilical trocar were closed. No suction drains were left in the subhepatic space at the end of the procedure.

In principle, all patients were subjected to a standard anaesthetic regime. As premedication, patients received Paracetamol 1000 mg supp., and Atropine 0.5 mg i.m.. Patients < 60 years and > 60 kg received Diazepam 10 mg p.o.; patients > 60 yrs. and < 60 kg received Diazepam 5 mg p.o.. Peri-operative anaesthesia, consists of Propofol 1.5 – 2.5 mg/kg, Sufenta 0.25 µg/kg, and Rocuronium 0.6 mg/kg. Standard postoperative analgesics were Paracetamol 4 dd. 1000 mg supp. and Morfine 6 dd. 10 mg sec during the first 48 hours postoperatively, until patients indicated pain was acceptable. If necessary, patients received additional Diclofenac 2 dd. 100 mg supp..

Retrospectively, medical records were checked for preoperative comorbidity, sphincterotomy, demonstrated biliary stones, conversion, complications, early postoperative pain and use of analgesics (during admission), postoperative complications, and health care consumption.

Self-report information

Preoperatively, during the patients' first surgical consultation, patients received the first set of questionnaires and signed informed consent. Patients completed and returned the first questionnaires before admission. After this baseline measure, patients completed the same questionnaires at ten days, six weeks, six months, and one year after cholecystectomy. Questionnaires contained self-report information on symptoms, pain, trait – and state anxiety, depressive symptoms, fatigue, and QoL.

Demographic variables were obtained preoperatively and patients completed a questionnaire that asked about sex, age, marital status, educational level, and work. Symptoms were investigated by a symptom checklist based on information from focus

groups, clinical experience, and another checklist[12]. Symptoms were categorised into biliary symptoms (upper abdominal pain, nausea, vomiting)[12], dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence)[12], and non-specific symptoms (general malaise, fatigue, weight-change, decrease in sexual functioning, and health complaints not mentioned in the pre-defined checklist). Patients described the nature, severity, duration, and frequency of pain during preoperative biliary attacks on a 100 mm. visual analogue scale (VAS) and on three multiple choice items.

Trait and state anxiety were measured with the Dutch versions of the STAI trait scale[54]. This questionnaire consists of two scales of 20 items each with a 4-item Likert-scale reflecting the extent of anxiety patients feel at a specific moment in time (state anxiety) and patients generally feel (trait anxiety)[54]. The STAI has good and moderate test-retest reliability for State anxiety (r = .84 – .88) and trait anxiety (r = .30 – .73)[60]. The state- and trait anxiety scales have high internal consistencies (Cronbach's α = .93 – .96) and (Cronbach's α = .92 – .93), respectively)[54, 60].

Depressive symptoms were assessed by the Center of Epidemiological Studies Depression Scale (CES-D)[61]. The CES-D has a 4-point Likert-scale indicating how often patients had experienced depressive symptoms in the week before. The 16-item version used in this study measures two independent factors, namely Depressed Affect and Positive Affect, and is a valid measure for depressive symptoms in the general population[61]. The CES-D has good internal consistency (Cronbach's α = .75 – .88).

Patients also completed the Fatigue Assessment Scale (FAS)[62], which consists of 10 items with a 5-point rating scale indicating how often patients usually feel tired. The FAS has an excellent internal consistency (Cronbach's α = .90) and good reliability[62, 63].

QoL was measured with the WHOQOL-BREF, which is a short version of the generic multi-dimensional WHOQOL-100, which was originally developed by the World Health Organization[38]. The WHOQOL-BREF consists of 26 items with a 5 point Likert-scale measuring QoL on in four different domains (Physical, Psychological, Social, and Environment). Two benchmark items display overall QoL and general health. The WHOQOL-BREF has been cross-culturally validated and has good psychometric properties, such as good internal consistency (Cronbach's α > .70) and adequate test retest reliability, constructive and discriminative validity[64, 65, 66, 67]. Self-reported information of patients, obtained preoperatively and at different time-points up to 12 months, formed the basis of the research described in this thesis.

Outline of this thesis

This thesis describes the systematic investigation of outcomes at different post-cholecystectomy intervals. Clinical and psychosocial variables were assessed as predictors of symptomatic outcome and QoL.

In **chapter 2** symptomatic outcome at six weeks after cholecystectomy was investigated. Predisposing factors for persistent and emergent biliary and dyspeptic symptoms were identified among clinical and demographical variables.

Chapter 3 contains an examination of symptomatic outcome and health care consumption six weeks after cholecystectomy. In addition to preoperative clinical symptoms and demographical variables, personality (i.e. trait anxiety) was investigated as a predictor of persisting and emerging symptoms.

In **chapter 4**, postoperative outcome was evaluated at six months after cholecystectomy. Preoperative clinical symptoms, demographic variables and TA were investigated as predictors of symptoms and pain at six months.

In **chapter 5**, we used a different categorization of preoperative symptoms in order to fit our design to the demands of clinical practice. Three profiles of preoperative symptoms were discerned, namely biliary symptoms only, dyspeptic symptoms only, and a combination of biliary and dyspeptic symptoms. Symptomatic change was investigated in the course of six months. Predictors were identified for several outcomes, namely the report of any symptom, of biliary symptoms only, of dyspeptic symptoms only, and of a combination of biliary and dyspeptic symptoms. Recommendations have been formulated for the approach of patients in daily practice.

Chapter 6 concerns the assessment of symptomatic outcomes at one year after cholecystectomy. A short evaluative index of overall QoL and health was added to gain insight in the subjective experience of patients. Predictors of symptomatic outcome and QoL at one year were identified among clinical variables and trait anxiety.

In **chapter 7**, the patient's subjective evaluation is highlighted, as a complete QoL measurement was integrated in the design. Changes in QoL and psychosocial variables were investigated and predictors of QoL one year after cholecystectomy were identified among clinical and psychosocial variables.

In the general discussion and summary (**chapter 8**) the main findings of this thesis are summarized and integrated and methodological issues are raised. This chapter further provides implications for future research and clinical practice.

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Chapter 2

Prospective six weeks follow-up post-cholecystectomy: The predictive value of preoperative symptoms

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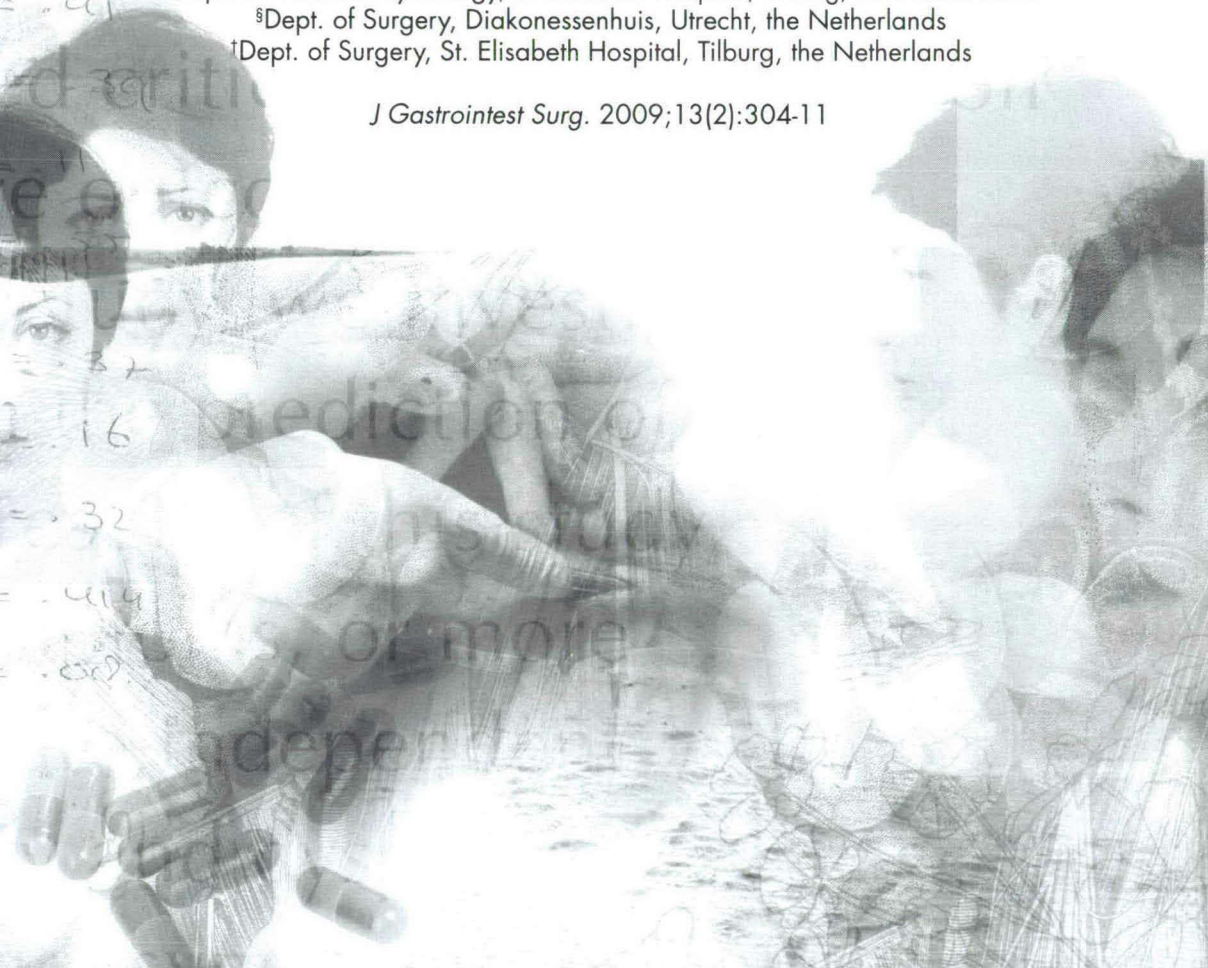


Abstract

Objective: Many patients with symptomatic cholelithiasis report persisting symptoms after elective cholecystectomy. The current prospective follow-up study aims at the identification and valuation of risk factors for negative symptomatic outcome at six weeks.

Methods: Consecutive patients (n = 183), age 18 – 65 years, indicated for elective cholecystectomy due to symptomatic cholelithiasis, completed a self-report questionnaire. At six weeks postoperatively, the same self-report questionnaires were completed (n = 129). Predictors of the persistence and emergence of biliary – and dyspeptic symptoms at six weeks post-cholecystectomy were investigated using univariate and multivariate logistic regression.

Results: At six weeks postoperatively, the report of postoperative biliary symptoms was independently predicted by preoperative dyspeptic symptoms (OR = 6.60) and bad taste (OR = 3.55). Preoperative flatulence was an independent predictor of the report of biliary and dyspeptic symptoms ((OR = 3.33) and (OR = 3.27), respectively) and persisting biliary symptoms (OR = 4.21). Predictors of symptomatic outcome were only identified in women, not in men.

Conclusion: Patients with preoperative dyspeptic symptoms, notably bad taste and flatulence, have an increased risk of negative post-cholecystectomy outcomes at six weeks. A symptom-specific approach should lead to optimalisation of the indication of cholecystectomy and information of patients. Known risk factors for long term outcomes might be valuable in female patients only.

Introduction

Gallstone disease (cholelithiasis) is a common condition in the Western world. In the Netherlands, 32,000 patients are yearly diagnosed with this condition[1]. The majority of patients remain asymptomatic and only 20% of patients develop clinical symptoms[2-4]. Symptomatic gallstone disease is typically diagnosed after an episode of biliary pain, which is defined as a severe steady pain, lasting more than 15 – 30 minutes, usually located in the epigastrum and/or right upper quadrant, sometimes radiating to the back[2, 5], which is often accompanied by dyspeptic symptoms[6-9]. However, some patients experience mild dyspeptic symptoms without biliary colics[10]. Additional ultrasonography is recommended[2, 9, 11], as clinical symptoms are not consistently related to the presence of gallstones[11-14]. Professional guidelines propose conservative treatment (wait and see) in asymptomatic cholelithiasis[2, 9, 15] and cholecystectomy in symptomatic cholelithiasis. In biliary pain without stones, cholecystectomy is occasionally indicated[10] following additional surgical consultation[2].

Elective cholecystectomy is widely performed in 70% of the symptomatic patients[16]. In the Netherlands, cholecystectomy is performed in 19,000 patients a year[1]. The majority of patients report positive outcomes, and relief rates for biliary pain (86% – 96%), upper abdominal pain (66% – 77%), and dyspepsia (46% – 89%)[13] are high. However, a substantial group of patients report persistence of pre-existent biliary (5.5% – 19.5%) and dyspeptic symptoms (27.3% – 43.2%)[8, 17, 18]. Thus, recognition of patients with a high risk of negative outcomes is crucial.

In literature, preoperative dyspeptic symptoms, the use of psychotropic medication, and a long history of pain, symptoms, and biliary attacks, are mentioned as potential predictors of poor outcome and persisting pain[17-19] at six months post-cholecystectomy. Although clinical experience indicates that most patients experience a major reduction of symptoms at six weeks post-cholecystectomy[20], no studies have explored predictors of symptomatic outcome at this time-point. The present prospective follow-up study aims at the identification and the valuation of predictors of negative symptomatic outcomes at six weeks after cholecystectomy.

Methods

Patients

Between March 2006 and August 2007 all patients between 18 and 65 years with diagnosed cholelithiasis (diagnosis K80 from International Statistical Classification of Diseases and Related Health Problems (ICD-10)), awaiting an elective laparoscopic cholecystectomy at the department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands, were eligible for the study. Exclusion criteria were: patients with ASA III or IV, undergoing an emergency procedure or intended open cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases.

Procedure

During patients' visit to the outpatient clinic, the surgeon performed a physical examination and explained the surgical and anaesthetic procedures. Patients were informed about the general prognosis after cholecystectomy and the risk of complications. Furthermore, the surgeon introduced the study and asked the patients to participate. Nurses informed patients further about the operation and the study, and handed out written information and the first set of questionnaires. Patients read the information at home and signed informed consent before participation.

Preoperatively, records were checked for medical history, comorbidity, and medication use. Before admission for cholecystectomy, patients completed the first questionnaires, which could be returned by mail or delivered to the nurses at the ward. In case the questionnaires were not returned five to three days before surgery, patients received a telephone call to remind them to complete the questionnaire. Patients who returned their first set of questionnaires after surgery were excluded from the study.

Six weeks after surgery, patients were sent another self-report questionnaire. Eight weeks and ten weeks after surgery, a phone call reminded the patients to return the postoperative questionnaire to the hospital, if necessary. The protocol of the study was approved by the local ethics committee.

Questionnaires and medical files

Questionnaires comprised self-reported demographic and clinical information. The demographic questionnaire asked about sex, age, marital status, educational level, and work. Furthermore, patients completed a self-constructed symptom-checklist, which asked about the presence of symptoms in the past week. Symptoms were collected from biliary patients participating in focus groups. Following a study of Weinert et al.[17], symptoms were categorized into symptom complexes, namely biliary symptoms (upper abdominal pain, nausea, vomiting), dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea and flatulence), and non-specific symptoms (general malaise, fatigue, weight-change, decrease in sexual functioning and other health complaints not-mentioned in the checklist). Medical files were checked for the experience of biliary and dyspeptic symptoms ever before visiting the outpatient clinic. After surgery, surgical reports were checked for the presence of gallstones/ sludge and conversion to open surgery.

Surgical and anaesthetic procedure

Open introduction was performed in all patients regardless of previous abdominal surgery. Pneumoperitoneum was created using the subumbilical trocar with an intra-abdominal pressure up to 12 mmHg. Three trocars for instruments were inserted. The dissection of the cystic artery and cystic duct, identifying Calot's triangle, was performed using a three points 'flag' technique. The cystic duct and artery were clipped and transsected. After complete dissection of the gallbladder, it was removed either through the subumbilical or subxyphoidal trocar. Fascia defects as a result of the insertion of the 10 mm trocar and the open introduction of the subumbilical trocar were closed. No suction drains were left in the subhepatic space at the end of the procedure.

In principle, all patients were subjected to a standard anaesthetic regime. As premedication, patients received Paracetamol 1,000 mg supp., and Atropine 0.5 mg i.m.. Patients < 60 years and > 60 kg received Diazepam 10 mg p.o.; patients > 60 yrs. and < 60 kg received Diazepam 5 mg p.o.. Peri-operative anaesthesia, consists of Propofol 1.5-2.5 mg/kg, Sufenta 0.25 µg/kg, and Rocuronium 0.6 mg/kg. Standard postoperative analgetics were Paracetamol 4 dd. 1000 mg supp. and Morfine 6 dd. 10 mg sec during the first 48 hours postoperatively, until patients indicated pain was acceptable. If necessary, patients received additional Diclofenac 2 dd. 100 mg supp.

Statistical analyses

Preoperative differences between responders (patients who returned their questionnaires at six weeks) vs. non-responders and dropouts (patients who ended participation within six weeks) were investigated by Chi-square tests (using Fisher's Exact test when appropriate) and Student's *t*-tests. Changes in symptoms were examined by the Mc Nemar test. Analyses were performed both for specific symptoms and symptom complexes.

Furthermore, persistence and emergence rates were calculated. Therefore, the population under study was divided in two subgroups categorised by the presence (group 1) or absence (group 2) of self-reported preoperative biliary – or dyspeptic symptoms. Patients with preoperative biliary symptoms (group 1) reported biliary symptoms only, or both biliary and dyspeptic symptoms. Patients without preoperative biliary symptoms (group 2) suffered from dyspeptic symptoms only. Likewise, patients with and without preoperative dyspeptic symptoms were categorised in two groups. Persistence was defined as reporting the symptoms both before and after cholecystectomy. Emergence was defined as not reporting the symptoms preoperatively, but reporting the symptoms at six weeks post-cholecystectomy.

To discern which preoperative symptoms predicted the postoperative report, the persistence, and the emergence of postoperative symptoms we used univariate logistic regression. Furthermore, significant univariate predictors of each outcome were entered in a multivariate regression model (method enter) to assess the relative strength of each predictor. In both outcome and predictors, we differentiated between symptom complexes and specific symptoms.

$P < .050$ indicated statistical significance. Statistical analyses were performed using SPSS version 14.0.1.

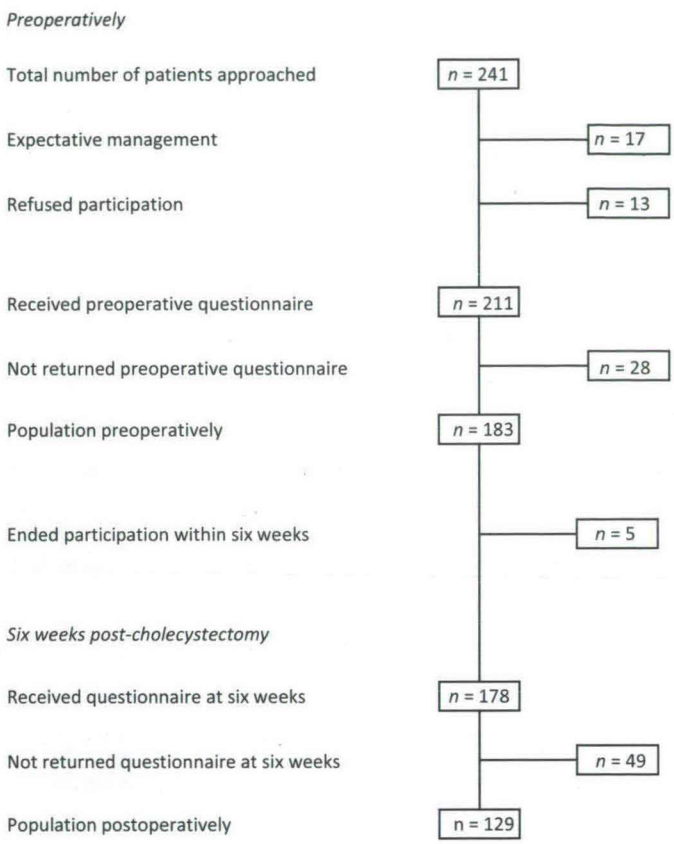
Results

Patient characteristics

Figure 1 provides an overview of the population across time. Of all 241 patients visiting the outpatient clinic and being approached for participation, 211 received the first questionnaire. Statistical analyses were performed on 183 patients (response rate 86.7%). Within six weeks, five patients ended participation. Six weeks after

cholecystectomy, data were available from 129 patients (response rate 70.5%). Because of missing values, final statistical analyses were performed on 126 patients.

Figure 1. Flow chart of the population in the course of six weeks.



In 94.0% of the patients biliary stones or sludge were demonstrated by ultrasonic tomography. Preoperatively, endoscopic sphincterotomy had been performed in eight patients. Laparoscopic cholecystectomy was converted to an open procedure in six patients. Table 1 shows the demographic and clinical characteristics of the patient group. Preoperatively, participants in the study did not differ from non-responders and patients who ended participation within six weeks. Among the participants, 74.3 % were females and the mean age was 46.0 ± 11.4 years. Female patients were younger than male patients (50.7 ± 9.6 yrs vs. 44.5 ± 11.6 yrs; (t = 3.30, p = .001)). Male patients more often reported urogenital diseases (p = .034) than female patients.

Preoperative symptoms

In the week before visiting the outpatient clinic, 73.6% of the patients experienced biliary symptoms and 66.7% of the patients experienced dyspeptic symptoms (table 1). Furthermore, 14.3% of all patients (n = 27) did not report any biliary - or dyspeptic symptoms. In the week before surgical consultation, female patients reported more preoperative biliary symptoms than male patients (78.5% vs. 59.6%, p = .019), whereas male patients more often reported to be free of symptoms than female patients (25.5% vs. 10.4%, p = .021). Moreover, examination of medical files revealed that 84.7% and 73.2% of the patients had ever experienced biliary- and dyspeptic symptoms. More specifically, 26.8% had experienced only biliary symptoms, 15.3% had experienced only dyspeptic symptoms, whereas 57.9% of the patients had ever experienced both biliary and dyspeptic symptoms. Patients reported a mean of 5.5 ± 7.7 biliary attacks. Preoperatively, upper abdominal pain was most frequently reported (66.5%), followed by nausea (39.3%) and flatulence (36.1%). Moreover, 55.2% of all patients reported non-specific symptoms. Female patients more often reported bad taste (χ^2 = 5.27, p = .022), upper abdominal pain (χ^2 = 4.25, p = .039), nausea (χ^2 = 9.70; p = .002), diarrhoea (χ^2 = 4.80, p = .029), and non-specific symptoms (χ^2 = 6.41, p = .011) than male patients.

Course of symptoms

In the time between the preoperative measurement and six weeks after cholecystectomy, five patients received an endoscopic sphincterotomy, of which two patients already received this procedure preoperatively. Furthermore, a general improvement was observed. The number of patients reporting biliary - and dyspeptic symptoms reduced to 25.4% and 50.8%, respectively ((χ^2 = 47.38, p < .001) and (χ^2 = 5.56, p = .018)). More specifically, the number of patients reporting bad taste, heartburn, upper abdominal pain, nausea, vomiting and under abdominal pain reduced significantly over six weeks time (see table 2). The percentage of patients reporting to be free of symptoms increased to 44.4% (χ^2 = 47.38, p < .001) (see figure 2).

Table 1. Baseline characteristics.

Demographic characteristics	
Female patients (%)	74.3
Age (M ± SD)	46.0 ± 11.4
Highest level of education	
Primary or lower vocational education (%)	20.6
Secondary education (%)	45.6
Higher education (%)	6.1
Higher professional education or university (%)	27.8
Working under payment (%)	72.4
Marital status	
Single (%)	6.1
Widowed or divorced (%)	6.6
Married or cohabitant (%)	87.3
Comorbidities	
Coronary arterial disease (%)	20.3
Pneumonal disease (%)	7.4
Abdominal disease (%)	25.0
Kidney diseases (%)	2.0
Urogenital diseases (%)	9.5
Neurological diseases (%)	11.5
Other comorbidities (%)	48.0
Self-reported medication use	
Analgesics (%)	37.8
Psychotropic medication (%)	10.1
Other medication (%)	46.7
Preoperative symptoms (self-reported)	
Cholelithiasis-specific (%)	73.6
Dyspeptic (%)	66.7
Free of symptoms (%)	14.3
Frequency of biliary colics (M ± SD)	5.47 ± 7.68
Demonstrated gallstones (%)	94.0
Preoperative symptoms ≤ 6 months (%)	68.3
Preoperative symptoms ≥ 7 months (%)	31.3

Chi square tests, Fisher's Exact Test, and Student's *t*-test were used to analyze preoperative patient characteristics.

* significance $p < .050$.

In spite of the general improvements over six weeks time, biliary symptoms persisted in 27.8% of the patients with preoperative biliary symptoms, whereas biliary symptoms emerged in 17.1% of the patients with only preoperative dyspeptic symptoms. Persistence of dyspeptic symptoms was reported in 57.3% of the patients with

preoperative dyspeptic symptoms. At six weeks, dyspeptic symptoms emerged in 38.6% of the patients who reported preoperative biliary symptoms only.

Symptom- and sex-specific patterns of the course of symptoms

At six weeks post-cholecystectomy, patients with and without demonstrated biliary stones and/or sludge, reported postoperative biliary and dyspeptic symptoms to the same extent. Subgroups of patients with and without preoperative biliary symptoms experienced postoperative dyspeptic symptoms to the same extent (45.7% and 52.2%, respectively). Furthermore, patients with preoperative dyspeptic symptoms reported postoperative biliary symptoms more often, than patients without preoperative dyspeptic symptoms (35.4% vs. 6.8%; $\chi^2 = 10.86$, $p = .001$).

Stratifying the self-reported improvements at six weeks post-cholecystectomy by sex, a different pattern of change was observed for male and female patients (see figure 3). Furthermore, no sex-bound patterns were found with regard to the emergence and persistence of biliary and dyspeptic symptoms after cholecystectomy.

Table 2. Self-reported symptoms preoperatively and six weeks after cholecystectomy (total population).

Symptoms	Baseline	Follow-up 6 weeks	*p*
	(*n* = 183)	(*n* = 126)	
Bad taste (%)	24.0	12.7	.001*
Heartburn (%)	25.1	15.1	.015*
Upper abdominal pain (%)	66.5	19.8	<.001*
Nausea (%)	39.3	13.5	<.001*
Vomiting (%)	14.8	3.2	.001*
Under abdominal pain (%)	24.6	8.7	.003*
Diarrhoea (%)	18.0	13.5	.839
Flatulence (%)	36.1	26.2	.082
Other health complaints (%)	55.2	46.8	.268

McNemar tests were used to analyze changes in symptoms over time.

* significance $p < .050$.

Figure 2. Pre- and postoperative symptoms in the total population.

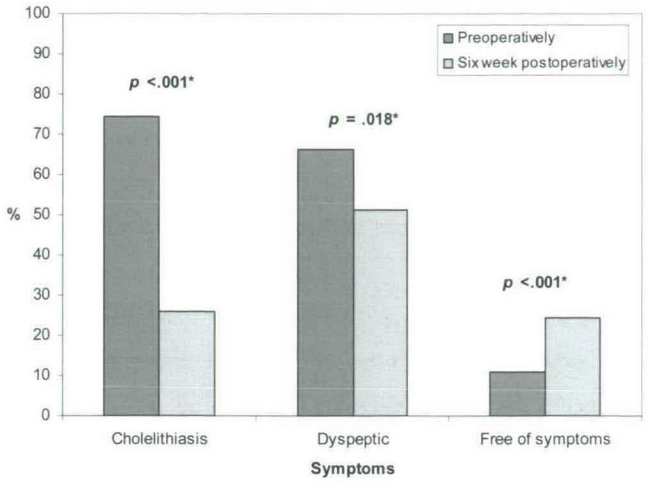
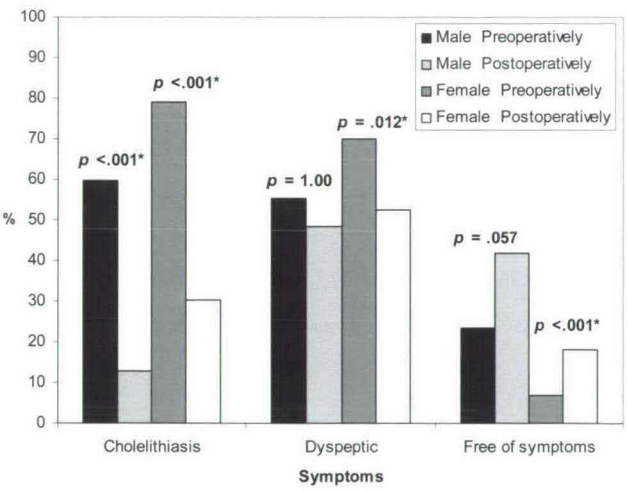


Figure 3. Course of symptoms over six weeks' time.



Preoperative symptoms in the prediction of symptomatic outcome

Univariate logistic regression analyses were used to identify the predictors of postoperative biliary – and dyspeptic symptoms, and the persistence and emergence of biliary – and dyspeptic symptoms (see table 3). Duration of preoperative symptoms and preoperative medication use were no significant predictors. No univariate predictors could be distinguished for the emergence of dyspeptic symptoms at six weeks.

The differential value of the identified predictors was further explored in multivariate logistic regression analyses, inserting the univariate predictors for each outcome as variables (method enter). The report of biliary symptoms at six weeks postoperatively was independently predicted by preoperative dyspeptic symptoms, bad taste, and flatulence (see Table 4). Both the report of postoperative dyspeptic symptoms and the persistence of biliary symptoms were independently predicted by preoperative flatulence. Other univariate predictors of postoperative symptomatic outcomes were non-significant.

Eligibility of preoperative symptoms in the prediction symptomatic outcome

First of all, sex-specific predictors were investigated by univariate logistic regression analysis (Table 5). Predictors of the postoperative report and the persistence of biliary – and dyspeptic symptoms were identified in female patients only, and not in male patients. In both men and women, no predictors were distinguished for the development of biliary – and dyspeptic symptoms. Moreover, the univariate predictors of each outcome were simultaneously entered in multivariate logistic regression analyses. These analyses could only be performed on the population of female patients. In female patients, the postoperative experience of biliary symptoms was independently predicted by bad taste only (*OR* = 3.73, *p* = .008; 95% *CI*: 1.42 – 9.84). At six weeks, the report of dyspeptic symptoms was predicted by heartburn and flatulence ((*OR* = 2.70, *p* = .040; 95% *CI*: 1.04 – 6.96) and (*OR* = 2.91, *p* = .020; 95% *CI*: 1.19 – 7.13), respectively). For the prediction of persisting biliary symptoms, no independent predictors could be identified.

Table 3. Univariate predictors of postoperative symptoms at six weeks (total population).

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Report of biliary symptoms	Dyspeptic symptoms	7.48	2.13 – 26.27	.002*
	Sex	4.10	1.15 – 14.58	.029*
	Bad taste	4.00	1.67 – 9.55	.002*
	Heartburn	2.38	1.01 – 5.60	.047*
	Nausea	2.38	1.05 – 5.38	.038*
	Flatulence	3.36	1.46 – 7.73	.004*
Report of dyspeptic symptoms	Dyspeptic symptoms	2.13	1.01 – 4.51	.047*
	Heartburn	2.60	1.14 – 5.95	.024*
	Flatulence	3.54	1.62 – 7.75	.002*
Persistent biliary symptoms	Dyspeptic symptoms	6.73	1.46 – 31.09	.015*
	Bad taste	3.69	1.37 – 9.96	.010*
	Flatulence	2.83	1.09 – 7.35	.033*
Emergent biliary symptoms	Flatulence	13.13	1.32 – 130.24	.028*
Persistent dyspeptic symptoms	Flatulence	3.28	1.32 – 8.17	.011*

Univariate logistic regression analysis was used to investigate the prediction of postoperative outcomes at six weeks post-cholecystectomy

* significance $p < .050$

Table 4. Predictors of postoperative symptomatic outcome (total population).

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Report of biliary symptoms	Dyspeptic symptoms	6.60	1.86 – 23.45	.005*
	Bad taste	3.55	1.38 – 9.17	.009*
	Flatulence	3.33	1.48 – 7.26	.004*
Report of dyspeptic symptoms	Flatulence	3.27	1.48 – 7.26	.004*
Persistent biliary symptoms	Flatulence	4.21	1.46 – 12.19	.008*

Multivariate logistic regression analysis was used to investigate the prediction of postoperative outcomes at six weeks post-cholecystectomy.

* significance $p < .050$.

Table 5. Univariate predictors of postoperative symptoms at six weeks (female patients).

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Report of biliary symptoms	Dyspeptic symptoms	5.29	1.45 – 19.28	.012*
	Bad taste	3.81	1.48 – 9.82	.006*
	Under abdominal pain	2.75	1.04 – 7.30	.042*
Report of dyspeptic symptoms	Heartburn	2.90	1.15 – 7.28	.024*
	Flatulence	3.09	1.29 – 7.43	.012*
Persistent biliary symptoms	Heartburn	2.94	1.08 – 8.05	.036*
	Flatulence	2.94	1.08 – 8.05	.036*
Persistent dyspeptic symptoms	Flatulence	3.15	1.15 – 8.60	.025*

Univariate logistic regression analysis was used to investigate the prediction of postoperative outcomes at six weeks post-cholecystectomy.

* significance $p < .050$.

Discussion

Most people with gallbladder stones never become patients, as they remain asymptomatic. Elective cholecystectomy is performed in 70% of patients with symptomatic cholelithiasis[16] aiming at a release from pain and symptoms and preventing complications. Postoperatively, a significant group of patients report persisting symptoms[17-19, 21-23]. Furthermore, cholecystectomy entails the risk of common bile duct injury and mortality in 0.5% and 0.2% of the patients, respectively[24]. Therefore, performance of elective cholecystectomy should be considered critically and recognition of patients with a high risk of negative outcomes is crucial. In this prospective follow-up study, we investigated the role of preoperative symptoms in the prediction of negative symptomatic outcome. The results of this study show that preoperative dyspeptic symptoms, or more specifically bad taste and flatulence, are independent predictors for the experience of biliary- and dyspeptic symptoms and the persistence of biliary symptoms. Although sex does not predict postoperative outcome, predictors are only identified in female patients.

In the current study, all abdominal symptoms decrease after cholecystectomy (with the exception of diarrhoea), which is also reported in studies with follow-up at six months[17, 25] or more than one year[23, 26]. In line with other studies[13, 17], greatest improvement was found for biliary symptoms, whereas dyspeptic symptoms more often persisted and emerged. At six months after cholecystectomy or later, biliary symptoms are found to be persistent in 5.6% – 20.0% of the patients[17] and dyspeptic symptoms are persistent in 10.0% – 40.2% of the patients[17, 23, 27]. In the current study we found higher percentages of 27.8% and 57.3% for persistent biliary and dyspeptic symptoms, which may be attributed to the timeframe of six weeks before follow-up. Approximately one third of the patients with biliary or dyspeptic symptoms only developed another type of symptoms at six weeks postoperatively. Although one study[17] reports a one-directional shift from preoperative biliary – to postoperative dyspeptic symptoms, the findings from the current study suggest a bidirectional shift from preoperative biliary symptoms to postoperative dyspeptic symptoms and vice versa.

As cholecystectomy is not beneficial to all patients, distinguishing patients with a heightened risk of persisting and emerging symptoms at six weeks is important. Literature mentions preoperative dyspeptic symptoms, preoperative flatulence, and experiencing over 3 symptoms of flatulent dyspepsia as predictors of negative post-

cholecystectomy outcomes, such as post-cholecystectomy syndrome and persistence of a bothersome symptom[17, 25, 28]. In addition, the current study asserts that preoperative dyspeptic symptoms, bad taste and flatulence are associated with a 3 to 7 times greater risk of postoperative biliary and dyspeptic symptoms. Furthermore, preoperative flatulence is associated with a 4 times greater risk of persisting biliary symptoms after cholecystectomy. Awareness of these risk-factors might have strong implications for clinical practice. Surgeons should be alert on the recognition of these patients during anamnesis and patients should be informed about their symptom-specific risk of negative post-cholecystectomy outcome. Furthermore, the existing knowledge on risk factors for negative symptomatic outcome should be integrated in clinical decision-making, with regard to guidelines for the indication of cholecystectomy and consideration of alternative treatment options.

Sex has an ambiguous position as a predictor of post-cholecystectomy symptomatic outcome. Although male sex is found to be a predictor of a 'not very successful' outcome[17] in literature, the current study indicates that sex is no predictor of self-reported symptoms or the persistence or emergence of these symptoms. However, predictors are only identifiable in female patients, and not in male patients. The latter point has implications for knowledge from the existing literature on predictors of post-cholecystectomy outcome. As the bulk of studies do not differentiate between male and female patients, we recommend a careful interpretation of results and the inclusion of the variable 'sex' in the design of future studies on cholecystectomy.

This study has several limitations. As this is a single-institution study, generalisation of the results to other health care centres might be limited. We investigated the predictive value of preoperative symptoms, taking biliary – or dyspeptic symptoms as feature of a clinical representation of cholelithiasis. Coinciding with biliary stones, dyspeptic symptoms are easily interpreted as a clinical feature of cholelithiasis. However, dyspeptic symptoms are quite common in the general population and may still be an isolated condition, even in the context of biliary stones. Therefore, although our results imply a relation between dyspeptic symptoms and postoperative outcome at six weeks, results should be interpreted with care. Unfortunately, we did not specifically investigate the combination of either both biliary and dyspeptic symptoms or the interaction between biliary – and dyspeptic symptoms on the prediction of six weeks symptomatic outcome. We recommend that this issue will be addressed in future research. Furthermore, this study investigated preoperative symptoms as predictors of

negative symptomatic outcome at six weeks post-cholecystectomy. Future studies should investigate the relation between symptomatic outcome at six weeks and long term outcomes, or the post-cholecystectomy syndrome. Despite the small sample of male patients (n = 46), we found a sex difference in terms of the impossibility to identify predictors of negative symptomatic outcome in male patients, in contrast to several predictors in female patients. Extensive exploration of predictors should be aimed at in a bigger sample of male patients and studies on predictors of long term post-cholecystectomy outcomes should integrate sex as a potential variable. Another shortcoming in this study is the fact that symptomatic outcome is a one-dimensional outcome, indicating the presence of symptoms only. Within this measure, differentiation should be sought by investigating severity and duration, implications for all day living, and psychosocial consequences.

In summary, at six weeks post-cholecystectomy, 27.8% and 57.3% of the patients reported the persistence of preoperative biliary and dyspeptic symptoms, respectively. Furthermore, 17.1% and 38.6% of the patients with only dyspeptic or only biliary symptoms developed another type of symptoms after cholecystectomy. Sex is no predictor of postoperative outcome, whereas preoperative symptomatology is. Patients reporting preoperative dyspeptic symptoms, bad taste, or flatulence have a heightened risk of experiencing postoperative biliary symptoms. Besides, patients with preoperative flatulence are at risk for the experience of postoperative dyspeptic symptoms and the persistence of pre-existing biliary symptoms. Management of cholelithiasis should be patient-tailored, thereby considering the prognosis after cholecystectomy differentially, based on the clinical presentation of preoperative symptoms. So far, predictors of postoperative symptomatic outcome have only been identified in female patients and not in male patients.

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Chapter 3

Trait anxiety predicts outcome six weeks after cholecystectomy

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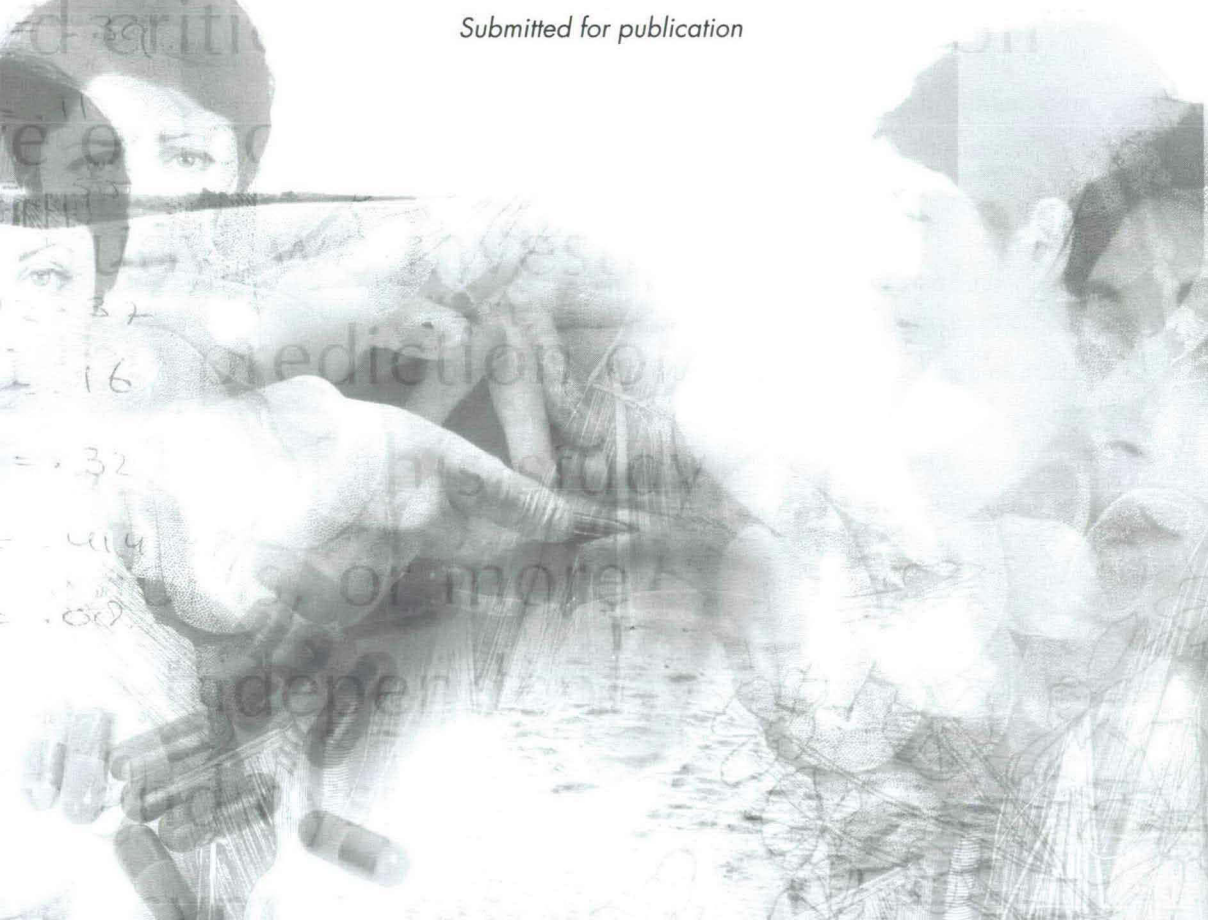


Abstract

Background: Surgical removal of the gallbladder (cholecystectomy) is the standard treatment in patients with gallstone disease. As many patients do not experience benefit from this procedure, early recognition of patients with a high risk of negative postoperative outcome is important. The aim of the current prospective follow-up study is to identify predictors (clinical symptoms and trait anxiety) of negative symptomatic outcomes at six weeks after cholecystectomy.

Methods: Consecutive patients (n = 133), ASA I and II, age 18-65 years, with symptomatic gallstone disease completed symptom-checklists and the STAI Trait-scale preoperatively and at six weeks after cholecystectomy. Cholecystectomy was performed under a standard surgical and anaesthetic regime. Risk factors were identified using univariate and multivariate regression analyses.

Results: Preoperative dyspeptic symptoms and High Trait Anxiety (HTA) predicted the experience of biliary symptoms at six weeks post-cholecystectomy (OR = 6.31) and (OR = .69), respectively). Only HTA predicted the persistence of biliary symptoms at six weeks (OR = 6.88). HTA and the number of preoperative dyspeptic symptoms both predicted the number of persisting biliary symptoms after cholecystectomy (β = .32 and β = .27, respectively).

Conclusions: In addition to clinical symptoms, HTA is a predictor of negative symptomatic outcome at six weeks after cholecystectomy. These findings suggest the need for a patient-tailored management of gallstone disease, based on specific personality traits like HTA. Tightening the indication for cholecystectomy in patients with HTA may reduce the number of unsuccessful cholecystectomies.

Introduction

Surgical removal of the gallbladder (cholecystectomy) is the standard procedure in case of symptomatic gallstone disease. Positive outcomes are reported after cholecystectomy, such as a relief of biliary pain (74% – 96%), a decrease of lower abdominal pain (66% – 91%), and less dyspepsia (46% – 89%)[1, 2]. On the other hand, cholecystectomy may lead to disappointing results as a substantial group of patients report the persistence and development of new symptoms and pain[2-7]. Early recognition of these patients is crucial to optimise clinical decision making in gallstone disease.

Poor cholecystectomy outcome is associated with clinical factors, such as comorbidity, heightened pain sensitivity, a long history of complaints (biliary pain, symptoms, attacks), preoperative dyspeptic symptoms, and use of psychotropic medication[2, 5, 8-12]. Stable personality traits, such as negative affectivity[13-15] and introversion[10, 15] also have an impact on several long- and short-term outcomes after cholecystectomy, such as medication use and pain. Trait Anxiety (TA)[16] is a relatively stable individual difference in the tendency to react with heightened anxiety to threatening situations, which remains stable between pre- and postoperative conditions[17]. The impact of TA on post-cholecystectomy recovery is indistinct[15, 17-19], as studies investigated small populations[15, 18, 19] and focussed on the first five days after cholecystectomy only. Evidence of the impact of TA on post-cholecystectomy outcome is further flawed as studies used different procedures and outcome variables, and controlled for different pre- and postoperative factors. We hypothesised that High Trait Anxiety (HTA) is a predictor for post-cholecystectomy recovery. As clinical experience learns that most patients report a relief of symptoms and return to work at six weeks after discharge[20], we investigated the impact of TA on symptomatic outcome at six weeks after discharge.

Methods

Patients

The current study was performed at the department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Between March 2006 and July 2007, consecutive patients (18 – 65 years) with diagnosed symptomatic gallstone disease, awaiting an elective laparoscopic cholecystectomy, were eligible for the study. Exclusion criteria were: patients with ASA III or IV, undergoing an emergency procedure or intended open

cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases. All patients were subjected to a standard surgical and anaesthetic procedure.

Procedure

The protocol of the study was approved by the local ethics committee. Preoperatively, surgeons introduced the study and asked the patients to participate in the study during the patients' visit to the outpatient clinic. Nurses further instructed the patients about the research procedures, and handed out written information and the first set of questionnaires. Patients signed informed consent before participation. Furthermore, records were checked for medical history, comorbidities, and medication use. Before admission for cholecystectomy patients completed and returned the first questionnaires. At five to three days before surgery, patients received a reminder telephone call to complete the questionnaire. Patients who returned their first set of questionnaires after surgery were excluded from the study. Six weeks after surgery, patients received the same self-report questionnaire by mail. Eight weeks and ten weeks after surgery, a phone call reminded the patients to return the postoperative questionnaire to the hospital, if necessary.

Questionnaires

The demographic questionnaire was completed preoperatively and asked about sex, age, marital status, educational level, work, and profession. Preoperatively and at six weeks after cholecystectomy, patients completed a symptom checklist, that asked about the presence of symptoms in the past week. Symptoms were obtained from clinical experience and information from focus groups. Categorisation of these symptoms was based on the study of Weinert et al.[6]. As symptomatic gallstone disease is traditionally diagnosed after right upper abdominal colicky pain, generally after the ingestion of food, sometimes accompanied by nausea and vomiting, these symptoms were subsumed as biliary symptoms. Peptic and lower abdominal symptoms, such as bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence, were categorised as dyspeptic symptoms. General malaise, fatigue, weight-change, decrease in sexual functioning, and other health complaints not mentioned in the pre-defined checklist were defined as

non-specific symptoms. All included patients had experienced biliary or dyspeptic symptoms before surgical consultation.

After surgery, surgical reports were checked for the presence of gallstones/ sludge and conversion for a laparoscopic procedure to open cholecystectomy, which is indicated in case of peri-operative complications. At six weeks postoperatively, medical reports were checked for mean time surgical consultations, visits to the emergency ward, and admissions to the hospital in relation to the cholecystectomy.

Patients completed the State-Trait Anxiety Inventory (STAI) preoperatively. The STAI-trait exists of 20 items with a 4-item Likert-scale reflecting the extent of anxiety patients generally feel. The STAI Trait Anxiety measure has good 3 months test-retest reliability (r = .75) and internal consistency (Cronbach's α = .84 – .92) [21]. Patients with a score above the 80th percentile were indicated as patients with 'High Trait Anxiety' (HTA).

Statistical analyses

Preoperative differences were investigated between responders (patients returning their questionnaires) and the group of non-responders and drop-outs (patients who ended participation < six weeks), using Chi-square tests and Student's *t*-tests. Further analyses were limited to the group of responding patients. Preoperatively, Chi-square tests, Student's *t*-tests, and Mann-Whitney *U* tests were used to observe differences between patients with and without HTA. If possible, effect sizes were calculated. Changes in the experience of symptoms over time, regarding the absence or presence of symptoms, were calculated using the McNemar Test with Chi-square or Binomial distribution when appropriate. Differences in the number of symptoms over time were investigated using Wilcoxon Signed Ranks Tests. Following Weinert et al.[6], analyses were performed for broad symptom complexes and specific symptoms.

Persistence of symptoms was defined as patients reporting a specific symptom or a complex of symptoms both before and after cholecystectomy. Emergence was defined as patients not reporting a specific symptom or a category of symptoms preoperatively, but reporting the experience of these symptoms at six weeks post-cholecystectomy. Persistence and emergence rates were calculated using frequencies. Predictors of the experience of postoperative symptoms and persistence of emergence of symptoms were calculated by univariate logistic regression and multivariate logistic regression, inserting sex, age, preoperative biliary, dyspeptic, and non-specific symptoms, and HTA (Method Enter). The number of postoperative symptoms experienced was investigated

using multiple linear regression analyses, entering HTA, sex, age and number of preoperative biliary, dyspeptic, and non-specific symptoms.

Statistical analyses were performed using SPSS version 14.0.1. $P < .050$ indicated statistical significance.

Results

In total, 239 patients were found eligible for this study. Six patients were not contacted before cholecystectomy, in 23 patients an expectative management was chosen, and 15 patients refused to participate. Preoperatively, 195 patients received the first questionnaire, which was not returned by 28 patients. In the course of six weeks, 6 patients ended their participation. At six weeks postoperatively patients received a second questionnaire, which 25 patients did not return. Only patients who returned their questionnaires both preoperatively and six week postoperatively were included (n = 136) (response rate 69.7%). Because of missing data, statistical analyses were performed on 133 patients. Clinical and demographic characteristics are shown in table 1. No differences were found between participating patients and patients who did not return their questionnaires or ended participation within six weeks. Preoperatively, 21.5% of the patients, more specifically 12.5% of the male patients and 24.7% of the female patients, had HTA (STAI-trait P ≥ 80). Patients with HTA did not differ from other patients on clinical and demographic characteristics.

All patients had biliary and / or dyspeptic symptoms before visiting the outpatient clinic. Gallstones or sludge were demonstrated in 90.4% and 8.8% of the patients, respectively. Preoperatively, sphincterotomy was performed in 5.1% of the patients. In five patients laparoscopic cholecystectomy was converted to an open procedure.

Pre- and postoperative symptoms and TA

Patients with HTA experienced more preoperative dyspeptic and non-specific symptoms than patients with lower levels of TA (U = 917.50, p = .037) and (U = 758.50, p = .001), respectively). HTA patients also reported more postoperative biliary (U = 734.50, $p < .001$) and non-specific symptoms (U = 735.00, $p < .001$), than patients without HTA.

Table 1. Baseline characteristics.

Demographic characteristics	
Male patients (%)	24.1
Age (M ± SD)	47.2 ± 12.1
Highest level of education	
Primary or lower vocational education (%)	21.5
Secondary education (%)	46.2
Higher education (%)	7.0
Higher professional education or university (%)	25.3
Working under payment (%)	67.4
Marital status	
Single (%)	5.4
Widowed or divorced (%)	5.4
Married or cohabitant (%)	89.2
Comorbidities	
Coronary arterial disease (%)	20.5
Pneumonal disease (%)	7.7
Abdominal disease (%)	27.4
Kidney diseases (%)	1.7
Urogenital diseases (%)	10.3
Neurological diseases (%)	9.4
Other comorbidities (%)	48.7
Preoperative symptoms	
Upper abdominal pain (%)	65.9
Nausea (%)	39.1
Vomiting (%)	16.5
Bad taste (%)	25.6
Heartburn (%)	26.3
Under abdominal pain (%)	22.6
Diarrhoea (%)	14.3
Flatulence (%)	35.5
General Malaise (%)	10.5
Fatigue (%)	46.6
Weight change (%)	3.0
Decreased sexual functioning (%)	7.5
Other health complaints (%)	13.5
Self-reported biliary symptoms (%)	72.0
Self-reported dyspeptic symptoms (%)	64.7
Self-reported non-specific symptoms (%)	54.1

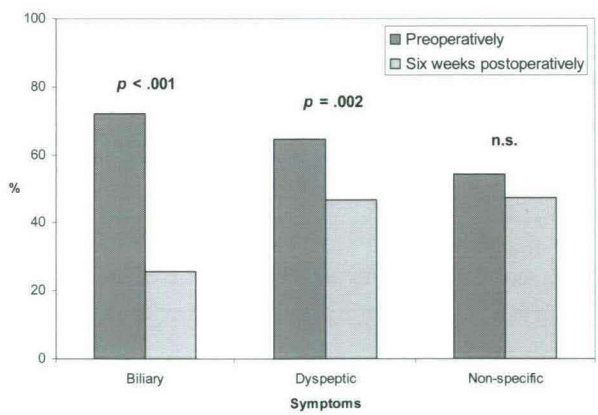
Health care consumption within six weeks

Ten days after cholecystectomy, the majority of patients (78.9%) paid a single visit to the outpatient clinic to check the healing of the wounds and to remove the sutures. However, 13.5% of the patients had one to three additional surgical consultations because of persistent pain or delayed healing of the wound. Moreover, within the first six weeks, 4.6% of the patients visited the emergency ward because of postoperative symptoms and 3.1% of the patients were admitted to the hospital within six weeks post-cholecystectomy. Differences were neither observed between patients with and without HTA, nor between patients with and without biliary, dyspeptic and non-specific symptoms.

Benefit of surgery

In the course of six weeks, biliary and dyspeptic symptoms reduced significantly (see figure 1). Still, postoperatively 25.6% of the patients reported biliary symptoms and 46.6% of the patients reported dyspeptic symptoms. The report of non-specific symptoms did not change.

Figure 1. Benefit at six weeks post-cholecystectomy (n = 133).



Differences in the experience of pre- and postoperative symptoms were calculated for patients with and without HTA ((n = 26) and (n = 95), respectively). In patients with HTA the experience of symptoms did not reduce significantly (Figure 2), whereas the number of patients without HTA experiencing biliary, dyspeptic, and non-specific symptoms reduced significantly over six weeks time (see figure 3). In patients without HTA, the

number of biliary (Z = - 6.72, p < .001), dyspeptic (Z = - 3.96, p < .001), and non-specific symptoms (Z = - 2.11, p = .035) dropped significantly over 6 weeks time. In HTA patients, the number of biliary (Z = - 2.11, p = .035) and dyspeptic (Z = - 2.70, p = .007) symptoms also reduced across time. However, in the latter group of patients the number of non-specific symptoms did not change over time.

Compared to patients without HTA, HTA patients more often reported the persistence of pre-existing biliary symptoms and the emergence of new biliary symptoms postoperatively ((18.6% vs. 57.9%, χ^2 = 10.704, p = .001) and (4.0% vs. 42.9%, χ^2 = 4.415, p = .025), respectively). Patients with and without HTA did not differ with regard to the report of persisting and emerging dyspeptic symptoms and persisting non-specific symptoms. However, at six weeks post-cholecystectomy HTA patients reported the emergence of new non-specific symptoms more often (95.0% vs. 49.0%; χ^2 = 10.93, p = .001).

Figure 2. Percentage of patients with High Trait Anxiety reporting pre- and postoperative symptoms.

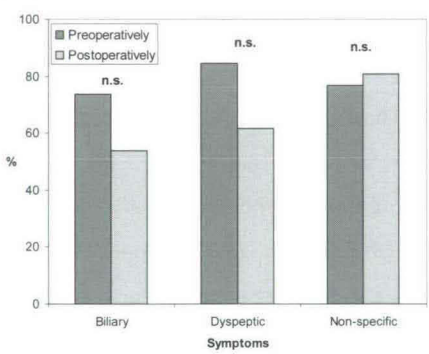
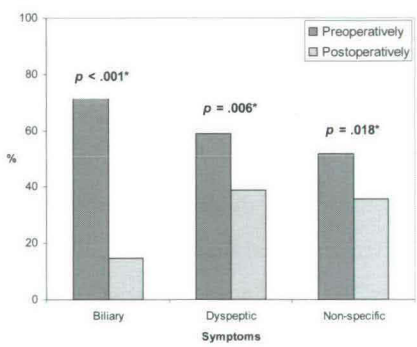


Figure 3. Percentage of patients without High Trait Anxiety reporting pre- and postoperative symptoms.



Prediction of postoperative symptoms

Univariate regression analyses identified HTA as a predictor of postoperative biliary (OR = 6.75, p < .001; 95% CI: 2.59 – 17.58), dyspeptic (OR = 2.51, p = .043; 95% CI: 1.03 – 6.12), and non-specific symptoms (OR = 7.54, p < .001; 95% CI: 2.61 – 21.79). Multivariate logistic regression analyses indicated that preoperative dyspeptic symptoms and HTA predicted the report of postoperative biliary symptoms (table 2). HTA was the only predictor of postoperative dyspeptic symptoms. Preoperative non-specific symptoms and HTA predicted the experience of postoperative non-specific

symptoms. Moreover, multivariate logistic regression analyses revealed that HTA was the only significant predictor of persisting biliary symptoms at six weeks after cholecystectomy. Preoperative biliary symptoms and HTA both predicted the persistence of non-specific symptoms. No predictors could be identified for the persistence of dyspeptic symptoms or the emergence of new symptoms at six weeks post-cholecystectomy.

Table 2. Predictors of symptomatic outcomes at six weeks post-cholecystectomy.

Symptomatic outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Report of biliary symptoms	Dyspeptic symptoms	6.31	1.31 – 30.38	.021*
	HTA	7.69	2.31 – 25.59	.001*
Report of dyspeptic symptoms	HTA	2.79	1.02 – 7.66	.047*
Report of non-specific symptoms	Non-specific symptoms	3.95	1.59 – 9.75	.003*
	HTA	6.56	1.98 – 21.75	.002*
Persistent biliary symptoms	HTA	6.88	1.78 – 26.58	.005*
Persistent non-specific symptoms	Biliary symptoms	5.22	1.03 – 26.45	.046*
	HTA	45.86	4.31 – 488.51	.002*

Multivariate logistic regression, method enter was used entering sex, age, HTA, preoperative biliary, dyspeptic, and non-specific symptoms as variables.

* Significance $p < .050$.

Multiple linear regression (entering sex, age, HTA, and the number of preoperative biliary, dyspeptic, and non-specific symptoms) demonstrated that HTA and the number of preoperative dyspeptic symptoms both predicted the number of biliary symptoms reported postoperatively (($\beta = .30$, $p = .001$) and ($\beta = .25$, $p = .007$), respectively). The number of preoperative dyspeptic symptoms was the only significant predictor of the number of postoperative dyspeptic symptoms ($\beta = .21$, $p = .047$). Furthermore, HTA and the number of preoperative non-specific symptoms both predicted the number of postoperative non-specific symptoms at six weeks (($\beta = .32$, $p = .002$) and ($\beta = .18$, $p = .037$), respectively).

Differentiating between persisting and emerging symptoms, we found that the number of persistent biliary symptoms was predicted by HTA ($\beta = .32$, $p = .003$) and the number of preoperative dyspeptic symptoms ($\beta = .27$, $p = .011$). No other predictors were identified. Furthermore, the number of biliary symptoms emerging after cholecystectomy was not predicted by any of the inserted variables. The number of preoperative dyspeptic symptoms predicted the number of persisting dyspeptic symptoms ($\beta = .26$, $p = .037$), whereas the number of preoperative non-specific

symptoms predicted the number of new dyspeptic symptoms emerging after cholecystectomy (β = .43, p = .017). HTA predicted the number of persisting non-specific symptoms (β = .36, p = .006), whereas the number of dyspeptic symptoms was a predictor of the number of non-specific symptoms that developed de novo at six weeks post-cholecystectomy (β = .38, p = .017).

Discussion

Although cholecystectomy is the golden standard to resolve biliary or dyspeptic symptoms in symptomatic gallstone disease, a substantial group of patients report persisting symptoms[4-6]. The key issue is to identify patients with a heightened risk of negative outcomes. This prospective follow-up study demonstrates that HTA has an impact on the experience of gallstone disease and recovery after cholecystectomy. Preoperatively, patients with HTA experience more dyspeptic and non-specific symptoms than patients without HTA. Moreover, the current study provides evidence that HTA has an impact on post-cholecystectomy recovery after controlling for differences in preoperative symptom report. At six weeks after cholecystectomy, both patients with HTA and preoperative dyspeptic symptoms have a seven times greater risk to report biliary symptoms. However, HTA is the only predictor of *persisting* biliary symptoms post-cholecystectomy, whereas preoperative symptomatology is not. Besides, HTA patients have a heightened risk to report postoperative dyspeptic and non-specific symptoms. Patients with dyspeptic symptoms are at risk to report new non-specific symptoms at six weeks after cholecystectomy. Despite differences in symptom report, health care consumption within the first six weeks post-cholecystectomy is similar for patients with and without HTA.

Preoperative symptoms are most thoroughly investigated as markers of negative outcomes after cholecystectomy. Dyspeptic symptoms, such as flatulent dyspepsia and diarrhoea, are mentioned as predictors of long-term negative outcomes (> 6 months)[6, 9, 10, 22, 23]. Findings of the current study indicate that other predictors might be of value *in addition to* these clinical symptoms. Moreover, in the current study, dyspeptic symptoms did not predict persistence of biliary symptoms, which is considered as the prominent feature of an unsuccessful cholecystectomy so far, but HTA did. However, the current study investigated recovery at six weeks after discharge, whereas the majority of

studies have focused on long term outcomes (> 6 months). We recommend that future studies investigate the impact of HTA on long term post-cholecystectomy outcomes.

Psychological factors, varying from psychopathological symptoms[9, 24] and social support[25] to personality traits[9, 10], are found to be associates of a lack of post-cholecystectomy improvement *next to* clinical characteristics. The current study demonstrates that, after controlling for clinical features, personality is the *only* predictor of persisting biliary symptoms at six weeks. The fact that other studies focused on long term outcomes (> one year), different outcome measures and psychological variables, may account for this difference. Previous studies on TA and post-cholecystectomy recovery[15, 17, 19, 26], based on small populations and with a focus on short-term post-cholecystectomy outcomes (maximum five days postoperatively), came to inconsistent results. Conversely, the current study, based on a bigger population, demonstrates that HTA is associated with several symptomatic outcomes at six weeks post-cholecystectomy. Additional research is needed to clarify the predictive qualities of TA and to gain insight in the mechanisms underlying the relation between HTA and postoperative recovery.

Generally, patients with HTA are known to have a higher pain sensitivity[27], which may result in an increased report of symptoms. However, as differences between patients with HTA and without HTA are primarily prominent at six weeks postoperatively, this explanation might not be viable. As TA is the tendency to interpret situations as threatening, patients with HTA are more vulnerable to experience (psychological) distress because of surgery. Higher, distress-related, levels of noradrenalin in patients with HTA[28] may lead to impaired wound healing and long lasting report of postoperative symptoms. Furthermore, diagnostic criteria for symptomatic gallstone disease are indistinct and patients with gastro-intestinal symptoms may erroneously be indicated for cholecystectomy. As HTA patients more often suffer from gastro-intestinal conditions[29], they may be at risk for poor decision making in cholecystectomy with negative symptomatic outcomes as a result.

This study has a prospective follow-up design, which enables us to follow the development of symptoms across time. As all patients (i.e. patients with and without symptoms at six weeks) were included in the preoperative measurement, the influence of confounding variables at six weeks postoperatively is minimised. As all consecutive patients visiting the outpatient clinic and matching the criteria for inclusion were eligible for the study, selection bias was avoided and generalisability to the general population

was optimised. Preoperatively, participants and patients who did not return the second questionnaire or ended participation (drop-outs) did not differ on demographic and clinical characteristics, the report of symptoms and HTA. Furthermore, participants and drop-outs did not differ from non-participants on demographic and clinical characteristics. However, a patient bias cannot be precluded as non-participants, who did not complete any of the measures at any time point in the study, may differ from participants on the report of preoperative symptoms and HTA. Moreover, in the current study we used a self-constructed symptom checklist to assess biliary, dyspeptic, and non-specific symptoms. This checklist was based on the existing literature, checklists, clinical experience, and information from focus groups. Preferably, a standard gastrointestinal symptom questionnaire, that is developed to measure the symptoms we were interested in, would have been used. However, existing questionnaires, such as the Gastrointestinal Symptom Rating Scale (GSRS)[30], are extensive and do not contain all symptoms specific for gallstone disease.

Another limitation of the present study is that we did not control for confounders, such as comorbidity. We investigated the influence of personality, more specifically HTA, in the context of clinically relevant variables, such as the presentation of symptomatic gallstone disease, age and sex. Further research should enable a broad insight in predictors of negative post-cholecystectomy outcome, thereby controlling for potential confounders. Six weeks after discharge is chosen as moment of follow-up, as clinical experience learns that most symptoms are relieved and most patients are able to go back to work as this time point[20]. We believe that this time point may be suitable as a first inventory of post-cholecystectomy outcomes. However, the results of this six weeks follow-up yet cannot be extended to long-term post-cholecystectomy outcomes or the post-cholecystectomy syndrome. Further research is needed to establish a relationship between HTA and long-term post-cholecystectomy outcomes and to corroborate the following recommendations.

Since HTA is associated with a heightened risk of negative post-cholecystectomy outcomes and approximately 20% of all patients have HTA, TA is a predictive factor worth paying attention to in clinical decision making. Information on TA could be easily obtained from a short self-report personality questionnaire, such as the STAI Trait Anxiety measure[31], which can be completed within five minutes during the patient's visit to the outpatient clinic. Integrating information about current symptoms, medical history, and level of TA, may be essential to come to a genuine patient-tailored approach

in gallstone disease. In patients with HTA, expectative management or alternative treatment options, such as biliary salts, should be considered besides cholecystectomy.

Cholecystectomy is widely performed in symptomatic gallstone disease, even though patients' and surgeons' expectations often are not met. Clinical decision making concerning cholecystectomy is often demanding, as the clinical presentation of symptomatic gallstone disease is often indistinct. In recent years, expectative management is gaining popularity in patients with endoscopic demonstrated gallstones and vague abdominal complaints. To reduce the amount of clinically unsuccessful cholecystectomies, guidelines for the indication of a cholecystectomy may be tightened, integrating new insights on the impact of personality. As cholecystectomy is a costly procedure [32], greater selectivity in the performance of cholecystectomies will lead to a greater cost-effectiveness in health care.

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Chapter 4

Trait anxiety predicts unsuccessful surgery in gallstone disease

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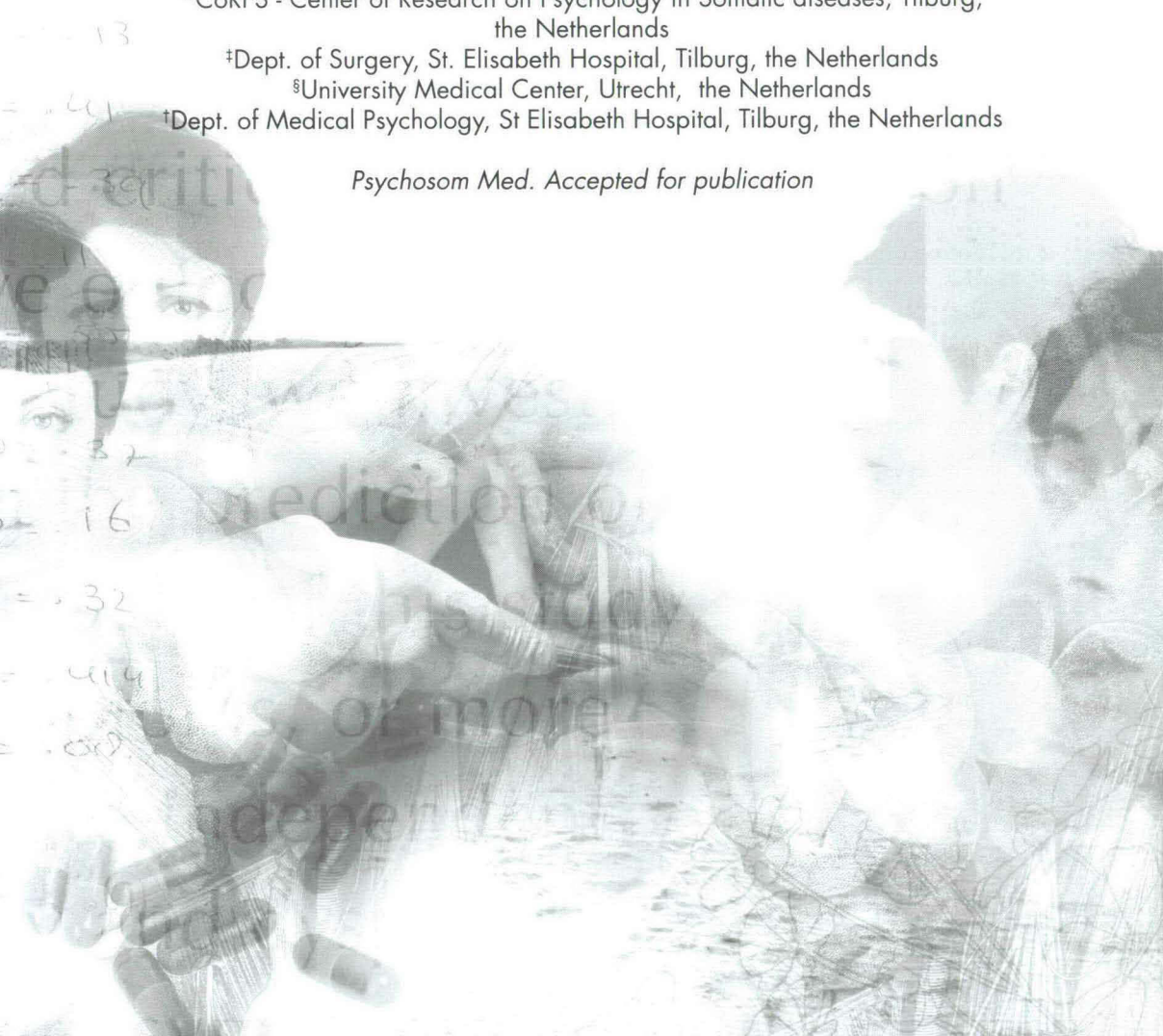


Abstract

Objective: Cholecystectomy (surgical removal of the gallbladder) is the preferred treatment in gallstone disease. After cholecystectomy, a substantial number of patients report persistence of symptoms. The aim of the study is to identify predictors of negative symptomatic outcomes at six months after surgery.

Methods: In this prospective follow-up study, consecutive patients (n = 172) diagnosed with symptomatic gallstone disease and indicated for elective cholecystectomy, were investigated. Preoperatively and at six months, patients completed self-report symptom checklists. The STAI trait scale was completed preoperatively and patients with a score ≥ P 80 were considered having High Trait Anxiety (HTA). Multivariate regression analyses were used to investigate independent predictors of persisting symptoms.

Results: Six months after cholecystectomy, HTA patients were more likely to report persisting biliary symptoms than patients without HTA (NHTA) (45.5% vs. 14.3%; χ^2 = 8.78, p = .002). HTA was identified as an independent predictor of persisting biliary symptoms at six months (*OR* = 3.08, p = .047; 95% *CI*: 1.02 – 9.34), in addition to the report of non-specific symptoms (*OR* = 6.16, p = .024; 95% *CI*: 1.27 – 29.82), and the use of psychotropic medication (*OR* = 4.76, p = .023; 95% *CI*: 1.24 – 18.34).

Conclusion: HTA patients have a three times higher risk at persisting biliary symptoms at six months after cholecystectomy, than NHTA patients. Both clinical factors and patients' personality should be considered in clinical decision making and risk estimation in elective cholecystectomy.

Introduction

Gallstone disease (cholelithiasis) is a common condition in the Western world[1, 2]. In the Netherlands, more than 30,000 patients yearly are diagnosed with gallstone disease[3]. Overall, 20% of all patients with gallstone disease experience clinical symptoms[4, 5]. Laparoscopic cholecystectomy (surgical removal of the gallbladder) is considered the golden standard in symptomatic cholelithiasis, beyond expectative management. Although the majority of patients report symptomatic benefit after surgery, such as a relief of all symptoms (53% – 81.5%)[6, 7], a relief of dyspeptic symptoms (56%)[8], and biliary pain (72%)[8], a substantial group of patients (40.4%)[9] does not experience any improvement after cholecystectomy. In many patients symptoms and pain persist (5.6% – 57.3%) or symptoms develop de novo postoperatively (12.0% – 38.6%)[10-17]. Moreover, cholecystectomy entails the risk of mortality (0% – 0.2%), complications (5.0%), and bile duct injuries (0.2% – 1.0%)[18]. As the risk of negative outcomes in cholecystectomy is considerable, performance of cholecystectomy should be considered carefully in each individual patient. Therefore, preoperative recognition of high-risk patients is crucial.

So far, risk assessment has emphasised the importance of clinical characteristics and symptoms. Preoperative dyspeptic symptoms[16, 19, 20], previous and current use of psychotropic drugs[17], characteristics of preoperative pain and symptoms[14, 19-21] (e.g. duration, level, nature), pain sensitivity, and age[21, 22] have been found as predictors of negative post-cholecystectomy outcomes. The patient's personality is found to predict several long and short term post-cholecystectomy outcomes[19, 22-25]. Personality is considered to be a set of relatively enduring traits and mechanisms that influence the individual's interactions with, and adaptations to, the environment. With respect to Trait Anxiety (TA), which can be defined as 'a relatively stable individual difference in anxiety proneness'[26], studies have focussed on short term outcomes (< five days post-cholecystectomy)[24, 25, 27] and found that TA predicted early postoperative pain[23], emotional and physical well-being[25] and the use of narcotics[23]. However, conclusive evidence could not be established due to the differential selection of procedures and outcome variables and the control for different pre- and postoperative variables. As we believe that personality is a predictor of long-term postoperative outcomes, we hypothesised that TA is a predictor of post-cholecystectomy outcomes at six months in addition to clinical symptoms.

Methods

Patients

Patients for the current study were recruited from the Department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Consecutive patients (18 – 65 years) with diagnosed symptomatic cholelithiasis, awaiting an elective laparoscopic cholecystectomy who visited the hospital between March 2006 and January 2008, were eligible for the study. Only patients with American Society of Anaesthetists (ASA) class I and II, i.e. healthy patients or patients with mild systemic diseases, were included. Patients undergoing an emergency procedure or intended open cholecystectomy, patients with choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases were excluded. Furthermore, as patients had to complete multiple questionnaires by themselves, patients with insufficient knowledge of the Dutch language were excluded. All patients underwent a standard surgical and anaesthetic procedure. The protocol of the study was approved by the local ethics committee.

Procedure

Preoperatively, participation was asked during the patients' first surgical consultation at the outpatient clinic. The surgeon introduced the study, whereas subsequently nurses informed patients about the research procedures. Patients received the first set of questionnaires, which also contained written information about the study, and signed informed consent. Medical history and comorbidities were obtained from medical records. Patients completed and returned the first questionnaires before admission for cholecystectomy. If necessary, patients received a reminder telephone call to return the questionnaires three to five days before the operation. Patients who returned the questionnaires after admission were excluded from the study. At six months after cholecystectomy, patients received the same questionnaire which could be returned in a prepaid envelope. If needed, patients were contacted by telephone twice, usually two and four weeks after sending the questionnaires. Patients returning their second questionnaire > 9 months after surgery were considered as non-responders.

Questionnaires

The demographic questionnaire was completed preoperatively and asked about sex, age, marital status, educational level, and work. Preoperatively and at six months post-cholecystectomy, patients completed a symptom checklist based on information from focus groups. Patients should tick off whether they experienced cholelithiasis-specific symptoms (upper abdominal pain, nausea, vomiting), dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence), and non-specific symptoms (general malaise, fatigue, weight-change, decrease in sexual functioning, and health complaints not mentioned in the pre-defined checklist) in the past week. Symptoms were considered as dichotomous items (yes/no) and were categorised following the study of Weinert et al.[14]. Furthermore, patients indicated the nature, severity, duration, and frequency of pain during preoperative biliary attacks on a 100 mm. visual analogue scale (VAS) and on three multiple choice items. All included patients had experienced biliary or dyspeptic symptoms in medical history. After surgery, surgical reports were checked for the presence of gallstones/ sludge and conversion to open surgery.

Patients completed the trait scale of the State-Trait Anxiety Inventory (STAI) preoperatively. The STAI-trait exists of 20 items with a 4-item Lickert-scale reflecting the extent of anxiety patients generally feel. The STAI Trait Anxiety measure has good three months test-retest reliability (r = .75) and internal consistency (Cronbach's α = .84 – .92)[28]. Patients scoring the 80th percentile or higher were indicated as patients with 'High Trait Anxiety' (HTA), whereas patients with a score below the 80th percentile were indicated as patients with 'Non High Trait Anxiety' (NHTA).

Statistical analyses

Preoperative differences between responders (patients returning their questionnaires) and patients that refused, ended participation within six months, or did not return their questionnaires on time, were investigated using Chi-square tests and Student's t tests with an adjusted alpha level (α = .0042) (Bonferroni correction) for multiple comparisons. Further analyses were limited to the group of responding patients. Preoperatively, Chi-square tests, Student's t tests, and Mann-Whitney U tests were used to observe differences between patients with HTA and NHTA and male and female patients. Bonferroni correction was applied to obtain a more stringent alpha level. As we computed group differences on 12 preoperative variables, i.e. the report (yes/no) and

the number of biliary, dyspeptic and non-specific symptoms, age, medication use, and sex or HTA, the alpha level was set at .0042. Postoperatively, group differences were computed for the report, the persistence, and the emergence (yes/no), and the number of biliary, dyspeptic, and non-specific symptoms reported at sis months. For this subset of 12 variables, the alpha level was also set at .0042. Changes in the experience of symptoms over time, regarding the absence or presence of symptoms, were calculated using the Mc Nemar Test with Chi-square or Binomial distribution when appropriate. Differences in the number of symptoms over time were investigated using Wilcoxon Signed Ranks Tests. Differences between HTA and NHTA patients over time were calculated using within-between ANOVA for repeated measures (Greenhouse-Geiser test for sphericity, repeated contrasts). Bonferroni correction was applied and the alpha level for these ANOVA's was set at .017.

All analyses were performed on broad categories of symptoms (biliary, dyspeptic and non-specific) following Weinert et al.[14]. Persistence of symptoms was defined as 'patients reporting a complex of symptoms both before and after cholecystectomy'. Emergence was defined as 'patients not reporting a category of symptoms preoperatively, but reporting the experience of these symptoms at six weeks post-cholecystectomy'. Persistence and emergence rates were calculated using frequencies. Predictors of the experience of postoperative symptoms, the persistence, and the emergence of symptoms were identified using univariate logistic regression. The report of preoperative biliary, dyspeptic and non specific symptoms was represented as a dichotomous (presence) and a categorical variable (number of symptoms). To serve clinical application, only the dichotomous variable was used in multivariate regression analyses. Multivariate logistic regression, inserting sex, age, preoperative biliary, dyspeptic, and non-specific symptoms, and HTA (Method Enter), was used to identify independent predictors of the report, the persistence and emergence of biliary and dyspeptic symptoms at six months. Collinearity was checked for this set of variables.

Statistical analyses were performed using SPSS version 17.0.1. $P < .050$ indicated statistical significance.

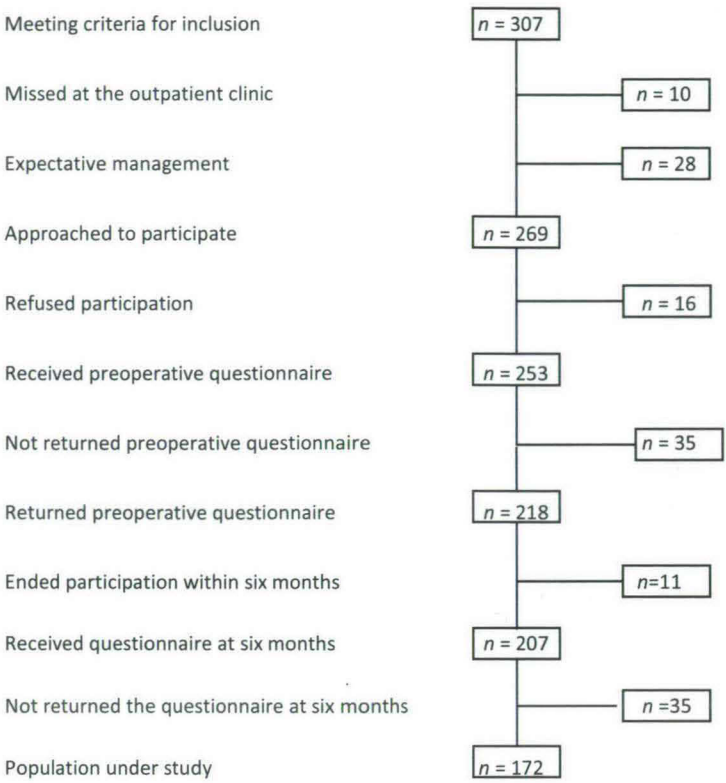
Results

Thirteen patients were excluded because of insufficient knowledge of the Dutch language. These patients did not differ in terms of gender and age from the patients in the sample. A flow chart of the population under study is shown in figure 1. In total, 307 patients visiting the outpatient clinic met the criteria for inclusion, of which 253 patients received the first set of questionnaires. At 6 months postoperatively, 172 patients returned their questionnaires (response rate 68.0%). Clinical and demographic characteristics of the population are shown in table 1. Preoperative symptoms are shown in table 2. Most commonly reported were biliary symptoms (74.4%), followed by dyspeptic (65.5%) and non-specific (56.1%) symptoms. Cholecystectomy was performed by surgeons and assistant surgeons in 27.9% and 72.1% of the patients, respectively. Laparoscopic cholecystectomy was converted to open surgery in 4.1% of the patients. Furthermore, differences were investigated between participants (n = 172) and patients that were missed, refused participation, or did not return the first set of questionnaires. Participants reported longer duration of symptoms than non-participants (χ^2 = 11.85, p = .003). Furthermore, differences were investigated between participants and patients that ended participation or not returned their questionnaires at six months. Participants were older (t = 3.18, p = .002) than drop-outs and non-responders at six months.

At baseline, patients with HTA and NHTA did not differ on demographic and clinical characteristics, reported the same frequency and nature of biliary attacks (in rest/movement), and reported the same level of pain during biliary attacks (VAS scores). Preoperatively, HTA patients reported more non specific symptoms (Z = - 3.65, p < .001) (see figure 2).

In addition to differences between HTA and NHTA patients, sex-differences were identified. Preoperatively, male patients were older than female patients (51.61 ± 9.53 vs. 46.23 ± 11.57; t = 2.99, p = .004). Furthermore, male and female patients reported the experience of preoperative biliary, dyspeptic, and non-specific symptoms to the same extent. Furthermore, female patients reported a greater number of biliary and dyspeptic symptoms ((.85 ± .83 vs. 1.36 ± .96, t = - 3.07, p = .002) and (.83 ± .93 vs. 1.38 ± 1.25, t = - 3.04, p = .003), respectively). The use of H-2 antagonists and proton pump inhibitors, pathology of gallstone disease, conversion to open cholecystectomy, and the level of surgical experience were not associated with the report (yes/no) and number of biliary, dyspeptic, and non-specific symptoms.

Figure 1. Flowchart of the population under study.



Impact of cholecystectomy

In the total population, the percentage of patients reporting biliary symptoms reduced in the first six months post-cholecystectomy from 75.6% to 17.2% (χ^2 = 85.50, p < .001). The number of patients reporting dyspeptic and non-specific symptoms reduced from 66.1% and 55.0% of the patients preoperatively to 49.7% and 37.0% at six months post-cholecystectomy ((χ^2= 12.85, p < .001) and (χ^2= 16.36, p < .001), respectively). Besides, the number of biliary and dyspeptic symptoms reported by patients also reduced significantly ((Z = - 8.81, p < .001) and (Z = - 5.32, p < .001), respectively). The number of non-specific symptoms did not change over time (Z = - .58, p = .565). At six months, the percentage of patients using proton pump inhibitors or H-2 antagonists decreased from 21.5% to 7.6% (χ^2= 14.69, p < .001). The preoperative use of H-2 antagonists and proton pump inhibitors, pathology of gallstone disease, conversion to open surgery, and level of surgical experience were not associated with the report (yes/no), persistence,

emergence, and number of biliary, dyspeptic, and non-specific symptoms reported at six months.

Table 1. Demographic and clinical characteristics (n = 172).

Demographic characteristics	
Female patients (%)	76.2
Age (M ± SD)	47.51 ± 11.33
Highest level of education	
Primary or lower vocational education (%)	17.1
Secondary education (%)	49.4
Higher education (%)	6.4
Higher professional education or university (%)	27.1
Working under payment (%)	68.8
Marital status	
Single (%)	4.1
Widowed or divorced (%)	5.9
Married or cohabitant (%)	90.0
Medical characteristics	
Self-reported medication use	
Analgesics (%)	36.8
Psychotropic medication (%)	9.9
Proton pump inhibitors / H-2 blockers (%)	21.5
Comorbidities	
Coronary arterial disease (%)	18.0
Pneumonal disease (%)	5.8
Abdominal disease (%)	22.1
Kidney diseases (%)	0.6
Urogenital diseases (%)	8.1
Neurological diseases (%)	9.9
Other comorbidities (%)	43.6

At six months after cholecystectomy, biliary symptoms persisted in 20.0% of the patients with preoperative biliary symptoms (n = 24). In this subgroup the number of biliary symptoms did not change over time (Z = - 1.80, p = .079). In total 7.5% of the patients without preoperative biliary symptoms reported new biliary symptoms at six months (n = 3). At six months post-cholecystectomy, 57.9% of the patients with preoperative dyspeptic symptoms (n = 62) reported persistence of these symptoms. Among these patients the number of dyspeptic symptoms reduced significantly (Z = - 3.63, p < .001).

At six months, 30.2% of the patients without preoperative dyspeptic symptoms (n = 16) reported new postoperative dyspeptic symptoms.

HTA and benefit form surgery

Six months after cholecystectomy, comparison of patients with HTA and NHTA showed that HTA patients more often reported biliary symptoms (36.7% vs. 12.5%; χ^2= 8.17, p = .004). HTA and NHTA patients reported the same amount of biliary, dyspeptic and non-specific symptoms (figure 2).

Among NHTA patients, the number of patients reporting biliary (χ^2= 76.01, p <.001), dyspeptic (χ^2= 9.50, p = .002) or non-specific symptoms (χ^2= 14.67, p < .001) dropped significantly over six months time. In addition, at six months post-cholecystectomy, the group of patients with HTA (n = 30) reporting biliary symptoms had decreased as well (p < .001). However, HTA patients reported dyspeptic symptoms to the same extent as before cholecystectomy (p = .11). Over six months time, the number of symptoms reduced both in patients with HTA and NHTA. Patients with NHTA reported a decrease of the number of biliary (Z = - 8.09, p < .001), dyspeptic (Z = - 4.68, p <.001), and non specific symptoms ((Z = - 3.51, p < .001). Patients with HTA also reported a smaller, but also a significant reduction of the number of biliary symptoms over time (Z = - 2.98, p = .003).

Investigating changes over time, within-between repeated measures ANOVA demonstrated a significant reduction of biliary symptoms across time (F = 78.96, p < .001). No main effect of HTA or interaction-effect of time and HTA was found. Performing a within-between repeated measures ANOVA, demonstrated a significant change of dyspeptic symptoms over time (F = 24.35, p < .001) and a significant effect of HTA (F = 9.52, p = .002). No significant interaction-effect was obtained. Concerning non-specific symptoms, time and HTA both had a significant effect ((F = 26.71, p < .001) and (F = 15.08, p < .001), respectively). Besides, an interaction effect was found between time and HTA (F = 5.79, p = .017).

At six months post-cholecystectomy, HTA patients more often reported persistent biliary symptoms than NHTA patients (45.5% vs. 14.3%; χ^2= 8.78, p = .002) (figure 3). Patients with HTA and NHTA reported persisting dyspeptic and non-specific symptoms to the same extent. The number of biliary, dyspeptic and non-specific symptoms remained constant in both patients with HTA and NHTA. With regard to the development of new symptoms, no differences were found between patients with HTA and NHTA.

At six months after cholecystectomy, men and women reported the persistence and emergence of biliary, dyspeptic, and non-specific symptoms to the same extent. At six months, no sex differences were obtained with regard to the number of biliary, dyspeptic, and non-specific symptoms reported.

Table 2. Preoperative characteristics of cholelithiasis and pathology.

Preoperative symptom report	
Category of symptoms	
Biliary symptoms* (%)	74.7
Dyspeptic symptoms§ (%)	65.5
Non-specific symptoms† (%)	56.1
Individual symptoms	
Upper abdominal pain (%)	66.5
Nausea (%)	40.4
Vomiting (%)	56.1
Bad taste (%)	21.6
Heartburn (%)	27.5
Under abdominal pain (%)	20.5
Diarrhoea (%)	18.7
Flatulence (%)	36.8
General malaise (%)	9.4
Fatigue (%)	49.7
Weight-change (%)	2.9
Decreased sexual functioning (%)	10.5
Other health complaints (%)	12.3
Duration of symptoms	
< 1 month (%)	19.2
1-6 months (%)	50.6
> 6 months (%)	30.2
Preoperative biliary attacks (M ± SD)	5.2 ± 7.2
Pain during biliary attack	
Pain in rest and movement (%)	100.0
VAS‡ pain severity in rest (M ± SD)	7.7 ± 2.4
VAS‡ pain severity in movement (M ± SD)	7.5 ± 2.6
VAS‡ pain duration in rest (M ± SD)	7.4 ± 2.5
VAS‡ pain duration in movement (M ± SD)	7.1 ± 2.7
VAS‡ pain frequency in rest (M ± SD)	6.9 ± 2.9
VAS‡ pain frequency in movement (M ± SD)	6.8 ± 3.1
Demonstrated stones or sludge (%)	91.9

Table 2. (continued)

Pathology	
Cholesterolosis (%)	2.9
Fibrosis or inflammation (%)	72.1
Both cholesterolosis and fibrosis / inflammation (%)	16.3
Adenoma / dysplasia / polyp (%)	.6
No abnormality (%)	2.3
Other pathology (%)	5.8

* ≥ 1 of the following symptoms: upper abdominal pain, nausea, vomiting.

§ ≥ 1 of the following symptoms: bad taste, heartburn, under abdominal pain, diarrhoea, flatulence.

† ≥ 1 of the folowing symptoms: general malaise, fatigue, weight-change, decreased sexual functioning, other health complaints.

‡ VAS = 100 mm. visual analogue scales

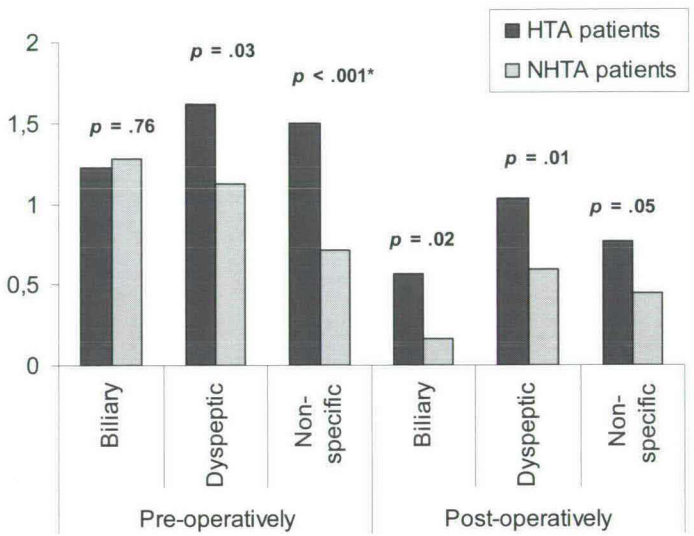
Prediction of six months symptomatic outcome

Univariate logistic regression analyses were used to identify predictors of reporting the presence, persistence, and development of new symptoms in the first 6 months after surgery. The report and the number of preoperative biliary, dyspeptic, or non-specific symptoms, sex, age, pathology of biliary disease, self-reported preoperative medication use and HTA were considered potential predictors of postoperative symptom report. The results of the univariate logistic regression analyses are shown in table 3. No predictors could be identified for the development of new biliary, dyspeptic, and non-specific symptoms at six months. Moreover, persistence of non-specific symptoms was not predicted by any of the potential predictors. HTA predicted the report of postoperative biliary symptoms and more specifically the report of persisting biliary symptoms. Sex and preoperative pain characteristics were not found to be predictive of outcomes at six months.

Multivariate regression analyses were performed (entering the univariate predictors for each differential outcome (see table 3)). The dichotomous variable that indicated the report of biliary, dyspeptic, or non-specific symptoms was entered in the multivariate regression, whereas the ordinal variable that indicated the number of biliary, dyspeptic, or non-specific symptoms was not. Results are shown in table 4. HTA predicts the report of biliary symptoms at six months, in addition to the clinical variables 'use of psychotropic medication' and 'report of non-specific symptoms'. The report of dyspeptic and non-specific symptoms at six months was predicted by clinical variables only, more specifically the report of dyspeptic and non-specific symptoms. Moreover, HTA predicted persistent biliary symptoms at 6 months, next to the report of preoperative

non-specific symptoms and the use of psychotropic medication. Persistent dyspeptic symptoms were predicted by preoperative non-specific symptoms only. After the insertion of 'sex' as an extra covariate in the multivariate regression analyses, exactly the same variables were identified as independent predictors of different outcomes at six months.

Figure 2. Mean number of symptoms in patients with HTA and NHTA.



Bonferroni correction was applied. $p < .0042$ indicated statistical significance.

Figure 3. Report of persisting symptoms at six months after cholecystectomy.

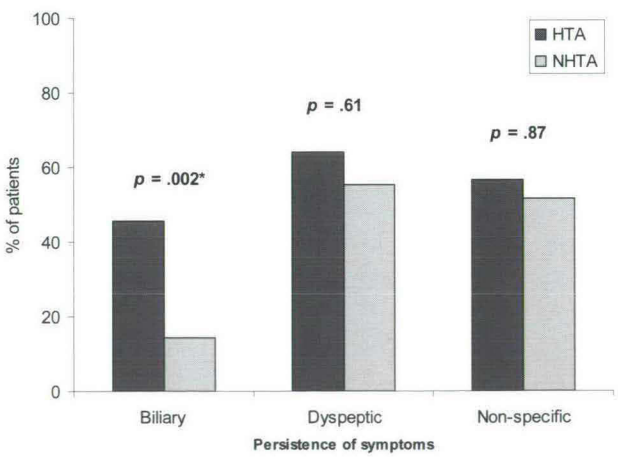


Table 3. Univariate predictors of postoperative symptoms (significant results reported only).

Symptomatic outcome at six months postoperatively	**Predictor**	***OR***	***95% CI***	***p***
Report of biliary symptoms	HTA	4.05	1.62 – 10.16	.003*
	Preoperative report of non-specific symptoms	5.33	1.75 – 16.26	.003*
	Number of preoperative non-specific symptoms	2.10	1.39 – 3.16	<.001*
	Preoperative use of psychotropic medication	5.47	1.89 – 15.83	.002*
Report of dyspeptic symptoms	Preoperative report of dyspeptic symptoms	3.19	1.58 – 6.42	.001*
	Number of preoperative dyspeptic symptoms	1.64	1.24 – 2.18	.001*
	Preoperative non-specific symptoms	2.61	1.36 – 4.98	.004*
	Number of preoperative non-specific symptoms	1.82	1.26 – 2.62	.001*
	Preoperative use of psychotropic medication	3.90	1.21 – 12.54	.022*
Report of non-specific symptoms	Preoperative dyspeptic symptoms	2.83	1.34 – 5.98	.006*
	Number of preoperative dyspeptic symptoms	1.46	1.11 – 1.91	.007*
	Preoperative non-specific symptoms	5.21	2.47 – 11.00	<.001*
	Number of preoperative non-specific symptoms	1.92	1.33 – 2.76	<.001*

Table 3. (continued)

Symptomatic outcome at six months postoperatively	Predictor	*OR*	95% *CI*	*p*
Persistence of biliary symptoms	HTA	5.00	1.80 – 13.93	.002*
	Preoperative report of non-specific symptoms	8.20	1.82 – 36.86	.006*
	Number of preoperative non-specific symptoms	3.06	1.26 – 7.45	.014*
	Preoperative use of psychotropic medication	6.18	1.85 – 20.66	.003*
Persistence of dyspeptic symptoms	Preoperative report of non-specific symptoms	2.53	1.13- 5.68	.024*
	Number of preoperative non-specific symptoms	1.63	1.07 – 2.47	.022*

Univariate logistic regression analyses were used to identify predictors.

* significance level $p < .050$.

Table 4. Multivariate predictors of postoperative symptoms (significant predictors only).

Symptomatic outcome at six months postoperatively	**Predictor**	***OR***	**95% *CI***	***p***
Report of biliary symptoms	HTA	3.15	1.16 – 8.55	.025*
	Preoperative use of psychotropic medication	5.18	1.40 – 19.21	.014*
	Preoperative report of non-specific symptoms	4.49	1.41 – 14.31	.011*
Report of dyspeptic symptoms	Preoperative report of dyspeptic symptoms	2.57	1.25 – 5.32	.011*
	Preoperative report of non-specific symptoms	2.28	1.16 – 4.51	.017*
Report of non-specific symptoms	Preoperative report of dyspeptic symptoms	2.41	1.09 – 5.31	.029*
	Preoperative report of non-specific symptoms	4.79	2.25 – 10.22	< .001*
Persistence of biliary symptoms	HTA	3.08	1.02 – 9.34	.047*
	Preoperative report of non-specific symptoms	6.16	1.27 – 29.82	.024*
	Preoperative us e of psychotropic medication	4.76	1.24 – 18.34	.023*
Persistence of dyspeptic symptoms	Preoperative report of non-specific symptoms	2.53	1.13 – 5.68	.024*

Multivariate logistic regression analyses were used entering univairate predictors for each outcome (see table 3).

* significance level $p < .050$.

Discussion

The current study demonstrated that many patients do not benefit from cholecystectomy. Indeed, at six months post-cholecystectomy, biliary and dyspeptic symptoms persisted in 20.0% and 57.9% of the patients respectively. Furthermore, in patients with only biliary symptoms, 30.2% of the patients had developed new dyspeptic symptoms at six months after surgery. In patients who presented gallstone disease with preoperative dyspeptic symptoms only, 7.5% developed new biliary symptoms after six months. We further investigated the predictive value of the personality trait HTA for six months post-cholecystectomy outcomes. Patients with HTA experienced a greater number of preoperative non-specific symptoms than patients with NHTA. Postoperatively, HTA patients were more likely to report biliary symptoms than NHTA patients. Both groups of patients showed a different profile of six month post-cholecystectomy recovery. Patients with HTA reported persistence of biliary symptoms more often than patients with NHTA. In case of persisting biliary symptoms, the number of symptoms reduced in NHTA patients, but not in patients with HTA. HTA patients have a three times higher risk of persisting biliary symptoms at six months post-cholecystectomy, than NHTA patients. Besides, patients with non-specific symptoms and patients using psychotropic medication have a five to six times higher chance of persisting biliary symptoms than patients without these preoperative characteristics. Persisting dyspeptic symptoms were not predicted by HTA, but were predicted by preoperative non-specific symptoms only.

Comparison with other studies

In literature, three other studies have focussed on follow-up at approximately six months[11, 14, 17]. These studies report persistence of biliary symptoms (nausea and vomiting) in 16.2% – 45% and 5.5% – 50% of the patients, respectively[11, 14, 17]. Although one study reported that biliary type pain had disappeared in all patients[11], we found that upper abdominal pain persisted in 12.8% of our respondents. Percentages of patients reporting persisting dyspeptic symptoms (57.6%) were comparable with results of other studies focussing on six months symptomatic outcome (27.3% – 60.0%)[11, 14]. Percentages of emerging biliary and dyspeptic symptoms at six months were also in line with literature[14] (1.7% – 9.2% and 9.6% – 24.5%, respectively). Comparability of the studies might be hampered by the use of different criteria in- or exclusion and the use of broad

categories of symptoms (indicating the presence of one or more symptoms) as dichotomous variable in the current study vs. individual symptoms in other studies. However, symptoms complexes are categorised in accordance with literature[14] and the use of these complexes facilitates the clinical application of the results.

So far, preoperative dyspeptic symptoms and the use of psychotropic medication are found to be predictors of short term[14, 16, 20] and long term[17, 19] negative outcomes after cholecystectomy. In accordance with previous studies, we found that psychotropic medication predicted the postoperative report and persistence of biliary symptoms only. Dyspeptic symptoms also had an impact on high symptom report at six months after cholecystectomy, but not on the persistence of pure biliary symptoms. Weinert et al.[14] found that dyspeptic symptoms predicted persistence of 'a single abdominal symptom subjectively rated as the most bothersome symptom'. This undifferentiating outcome is not comparable to the more objective outcome measures used in the current study. Furthermore, the present study identified the presence of preoperative non-specific symptoms as a predictor of negative symptomatic outcome at six months. To the authors knowledge, the impact of non-specific symptoms, which may be of psychosomatic origin, has not been investigated yet in relation to post-cholecystectomy outcomes. We believe that investigation of these symptoms may offer a new perspective to risk estimation in post-cholecystectomy recovery and well-being.

Other studies have identified preoperative pain characteristics (e.g. duration, level, nature, location) as predictors of postoperative outcomes[14, 19, 21]. The current study did not replicate these findings. Neither the often used VAS's, nor multiple choice items indicating the length, severity, and duration of preoperative pain, predicted postoperative persisting symptoms. As methods of pain measurement were different, this may indicate that the nature of pain measurement may be decisive for the outcomes. Likewise, in contrast to other studies[21, 22], the current study demonstrates that age is no risk factor for negative symptomatic outcome at six months. Moreover, Weinert et al.[14] found that male sex was a risk factor of persistence of the most bothersome symptom. Although preoperative sex differences were identified with regard to symptom report, sex was no predictor of symptomatic outcome at six months. In contrast to the findings of Weinert et al.[14], we also demonstrated that the use of H-2 antagonists and proton pump inhibitors was no univariate predictor of symptomatic outcome at six months.

The results of the current study indicate that personality, or more specifically Trait Anxiety which can be defined as 'a relatively stable individual difference in anxiety proneness'[26], has an impact on biliary symptoms reported at six months after cholecystectomy. HTA patients may be more sensitive to the experience of pain in general[28] and for gastro-intestinal symptoms[29] in particular, which might result in overall heightened symptom report in this study. However, our results suggest that HTA influences the persistence of biliary symptoms only. Postoperatively, HTA patients might misinterpret postoperative abdominal symptoms as persistent biliary symptoms. However, HTA patients might also objectively experience persistence of preoperative symptoms more often. As the relation between abdominal symptoms and demonstrated gallstones is difficult to establish[30] and the indication for cholecystectomy is not clear-cut, patients with long-lasting abdominal complaints may be operated on wrong indications resulting in persistence of their preoperative symptoms. As HTA patients more often experience gastro-intestinal symptoms, they are at risk for persistence of the same preoperative symptom. However, additional research is needed to corroborate these findings and to investigate the mechanisms of influence.

Strengths and limitations

The current study has some methodological advantages beyond other studies investigating predictors of post-cholecystectomy outcomes. As this study was performed under a prospective follow-up design and consecutive patients were approached, selection bias is limited and the control for confounding influences is optimized. However, we acknowledge that this is a single center study with a relatively small sample size, which may hamper generalisability of our results. Other studies in the field included non-consecutive patients[11, 23], patients with simply demonstrated gallstones[11], an indication for acute cholecystectomy[10, 17], or did not define criteria for in- and exclusion explicitly[14, 21]. The current study has a relatively homogeneous sample due to more restricted criteria for inclusion, namely patients with uncomplicated symptomatic gallstone disease with an indication for elective cholecystectomy. As a consequence, the findings are only applicable to a restricted field of surgery where consideration of pros and cons matters most: strictly elective procedures.

The results of this study on long-term post-cholecystectomy outcomes are preliminary. Up to now, research on TA has focussed on short term post-cholecystectomy outcomes (< five days), which has led to inconclusive evidence[23-25, 27]. The role of TA should be

investigated at longer follow-up (> 6 months) investigating the impact of TA on the development of the post-cholecystectomy syndrome and other long term outcomes, such as quality of life and health care consumption. Furthermore, knowledge on the impact of TA on other post-surgical outcomes and on the prevalence of abdominal symptoms in the general population may provide a context in which the results of this study could be better understood. These issues may be addressed in future studies. As patients were questioned preoperatively and at six months, the results of the study do not clarify whether symptoms actually persisted or recurred in six months time. No predictors could be identified for the development of biliary, dyspeptic and non-specific symptoms over time, possibly because of small sample sizes. Future research should aim at the course of symptoms over time, in an extended sample. Furthermore, findings of the current study may be flawed by the fact that we did not control for other medical conditions in the course of six months. Temporary health conditions that are not related to cholecystectomy, such as gastroenteritis, may influence the results at six months. Due to the use of a self-constructed, non-standardised symptom checklist, results of the current study are difficult to compare with other studies. Therefore, we plead for the construction of a disease-specific instrument that represents a uniform view on the symptomatology of gallstone disease and can be used to identify patients with a heightened risk of negative outcomes.

Implications

The outcomes of this study may have implications for clinical practice. Hitherto, considering the pros and cons of performing cholecystectomy, surgeons focus on preoperative symptomatology and information of ultrasound examinations only. The current study demonstrated that psychosocial variables, more specifically personality or HTA, have an impact on outcome after elective cholecystectomy. Therefore, clinical and psychological factors may be integrated to come to an improved risk estimation of negative post-cholecystectomy outcomes. Besides known clinical risk factors, such as the presence of preoperative dyspeptic symptoms, non-specific symptoms should be considered as an additional risk factors of negative symptomatic outcome at six months. Patients with HTA and non-specific symptoms should be informed about their heightened risk on negative outcome after an elective cholecystectomy. Ideally, clinical decision making should be based on comprehensive knowledge on personality and other

predictors of negative post-cholecystectomy outcomes. In future, clinical decision making in cholecystectomy may be tailored to the individual patient's risks and needs.

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Chapter 5

Risk assessment in cholelithiasis: Is cholecystectomy always to be preferred?

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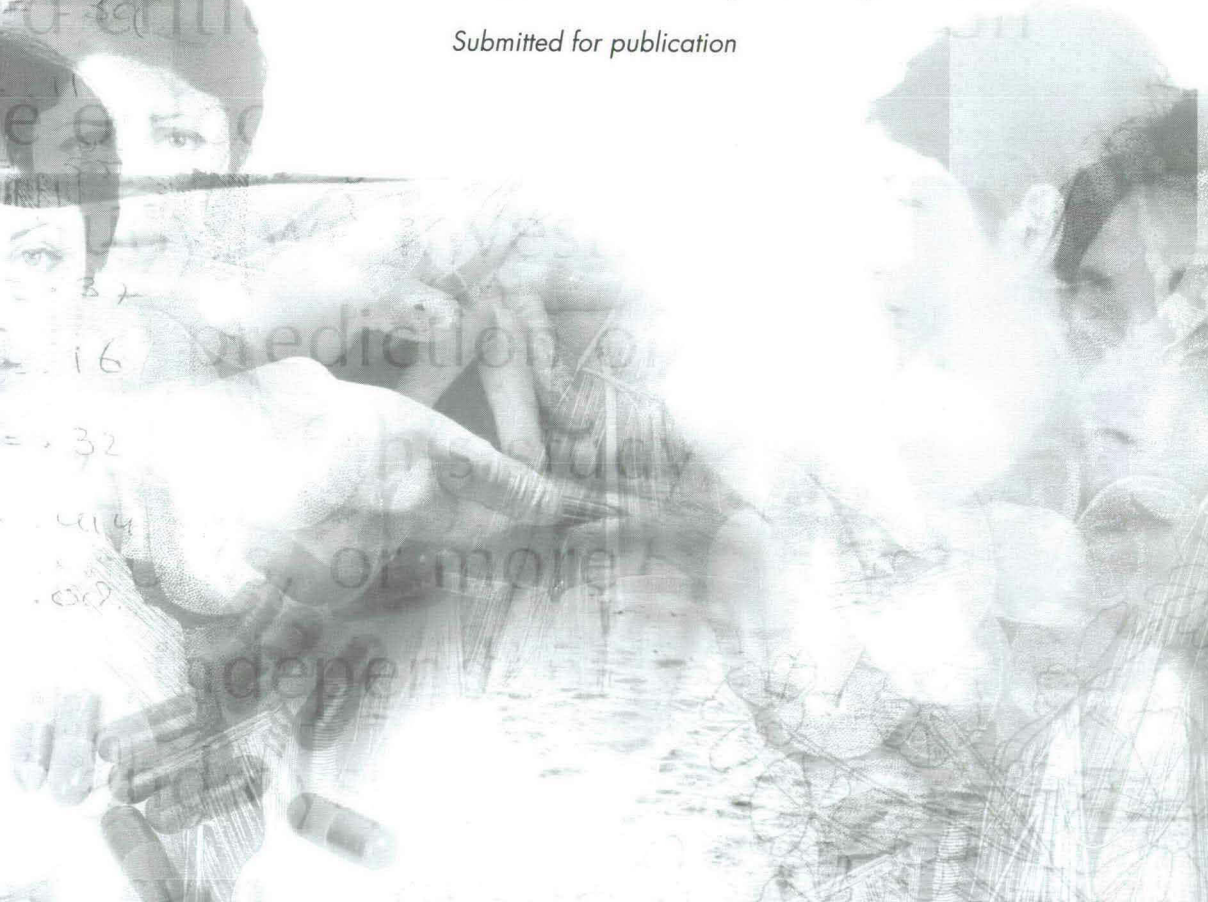


Abstract

Background and aim: Cholecystectomy is the standard procedure in symptomatic gallstone disease (cholelithiasis). As many patients with cholelithiasis do not benefit from cholecystectomy, pre-operative recognition of such high-risk patients is important. This study aims at the identification of predictors of persisting symptoms at six months after cholecystectomy for patients with different preoperative symptomatology.

Method: This prospective follow-up study was executed in a Dutch teaching hospital. Consecutive patients (n = 172), age 18 – 65 years, with symptomatic cholelithiasis, undergoing a laparoscopic cholecystectomy were investigated using self-report symptom checklists and questionnaires. Predictors were identified using uni- and multivariate regression analyses.

Results: At six months post-cholecystectomy, patients reporting only preoperative biliary symptoms were most often free of symptoms (62.5%). Non-specific symptoms predicted the report of post-operative symptoms in patients with only biliary or only dyspeptic symptoms ((*OR* = 6.11, *p* = .043; 95% *CI*: 1.06 – 35.35) and (*OR* = 4.53, *p* =.002; 95% *CI*: 1.77 – 11.60), respectively). Persistence of the pre-existing pattern of symptoms was predicted by the use of psychotropic medication (*OR* = 5.27, *p* = .010; 95% *CI*: 1.50 – 18.55) and dyspeptic symptoms (*OR* = 16.69, *p* < .001; 95% *CI*: 4.59 – 60.68). Postoperative biliary symptoms were predicted by High Trait Anxiety (HTA) (*OR* = 10.64, *p* = .031; 95% *CI*: 1.24 – 90.96).

Conclusion: The management of cholelithiasis should be based on individual-specific risks. Expectative management may be the first choice in patients with non-specific symptoms, with dyspeptic symptoms only, with HTA, and in patients using psychotropic medication.

Introduction

Gallstone disease (cholelithiasis) is a common condition that affects 5% to 22% of the people in Western countries[1, 2]. Most patients are unaware of their condition[3] and only 10% – 30% of these patients develop clinical symptoms[4-7], such as classical biliary colics or other gastrointestinal symptoms. Laparoscopic cholecystectomy is the golden standard in the management of uncomplicated symptomatic cholelithiasis. As cholecystectomy entails the risk of peri- and early postoperative complications (0.2% – 9.4%)[5, 8] and a substantial number of patients (40.4%) report negative outcome after cholecystectomy[9, 10], critical consideration of pros and cons of cholecystectomy is required. Identification of potential predictors of negative outcomes is essential for decision making in elective cholecystectomy.

Clinical characteristics, such as preoperative dyspeptic symptoms[11-13], medication use[10], age[14, 15], characteristics of preoperative pain and symptoms[12, 13, 15, 16] have been identified as associates of long- and short term post-cholecystectomy outcomes. However, the comparability of these results is hampered as studies used different criteria for inclusion, moments of follow-up, definitions and operationalizations of variables and outcomes. Besides 'hard', clinical characteristics, 'soft' predictors such as self rated health status[13], personality traits[12, 17-19], and other psychological variables[20] have been identified as predictors of negative outcomes as well. Despite the fact that the symptomatology of cholelithiasis is ambiguous and only the minority of patients report classical biliary colics[5, 21], preoperative symptoms (in combination with ultrasound examination) are used as a reference point for diagnosis and indication of cholecystectomy in clinical practice. Therefore, in the current study we aimed at the identification of predictors of postoperative symptoms at six months post-cholecystectomy for patients with different preoperative symptomatology.

Methods

Patients

Patients for the current study were recruited from the Department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Consecutive patients (18 – 65 years) with diagnosed symptomatic cholelithiasis, awaiting an elective laparoscopic cholecystectomy who visited the hospital between March 2006 and January 2008, were

eligible for the study. Exclusion criteria were: patients with ASA III or IV, undergoing an emergency procedure or intended open cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases. All patients underwent a standard surgical and anaesthetic procedure. The protocol of the study was approved by the local ethics committee.

Procedure

Preoperatively, participation was asked during the patients' first surgical consultation at the outpatient clinic. The surgeon introduced the study, whereas subsequently nurses informed patients about the research procedures. Patients received the first set of questionnaires, which also contained written information about the study, and signed informed consent. Medical history and comorbidities were obtained from medical records. Patients completed and returned the first questionnaires before admission for cholecystectomy. If necessary, patients received a reminder telephone call to return the questionnaires three to five days before the operation. Patients who returned the questionnaires after admission were excluded from the study. At six months after cholecystectomy, patients received the same questionnaire which could be returned in a prepaid envelope. If needed, patients were contacted by telephone twice, usually two and four weeks after sending the questionnaires. Patients who returned their second questionnaire > 9 months after surgery were considered as non-responders.

Questionnaires

The demographic questionnaire was completed preoperatively and asked about sex, age, marital status, educational level, and work. Preoperatively and at six months post-cholecystectomy, patients completed a symptom checklist based on information from focus groups and clinical experience. Patients should tick off whether they experienced biliary symptoms (upper abdominal pain, nausea, vomiting), dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence), and non-specific symptoms (general malaise, fatigue, weight-change, decrease in sexual functioning, and health complaints not mentioned in the pre-defined checklist) in the past week. Symptoms were categorised following the study of Weinert et al.[13]. Furthermore, patients indicated the nature, severity, duration, and frequency of pain during

preoperative biliary attacks on a 100 mm. visual analogue scale (VAS) and on three multiple choice items. All included patients had experienced biliary or dyspeptic symptoms in medical history. After surgery, surgical reports were checked for the presence of gallstones/ sludge and conversion to open surgery.

Patients completed the Trait scale of the State-Trait Anxiety Inventory (STAI) preoperatively. The STAI-trait exists of 20 items with a 4 item Likert-scale reflecting the extent of anxiety patients generally feel. The STAI Trait Anxiety measure has good three months test-retest reliability (r = .75) and internal consistency (Cronbach's α = .84 – .92)[22]. Patients scoring the 80th percentile or higher were indicated as patients with 'High Trait Anxiety' (HTA), whereas patients with a score below the 80th percentile were indicated as patients with 'Non High Trait Anxiety' (NHTA).

Statistical procedure

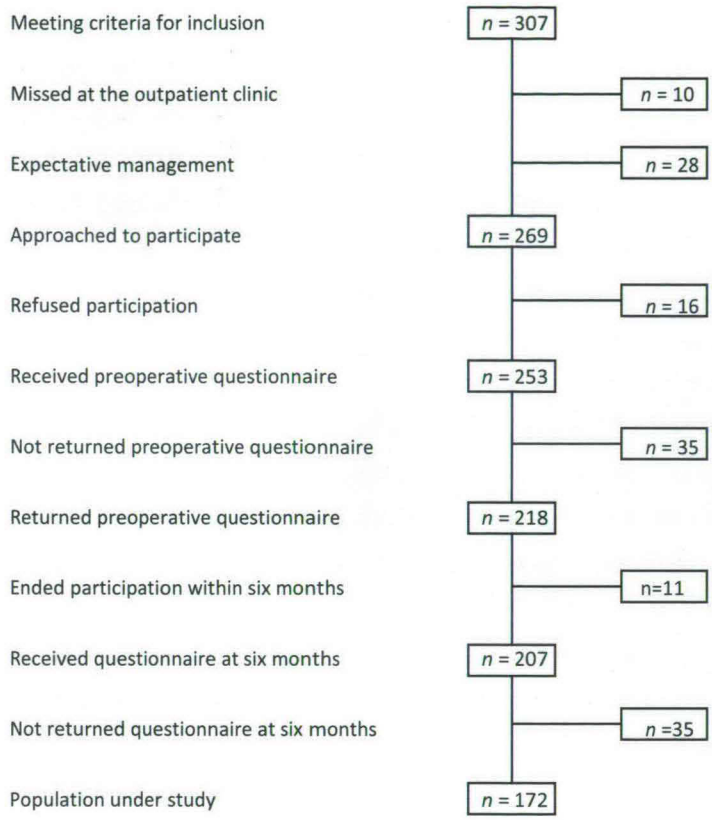
Differences between groups of patients with preoperative biliary, dyspeptic, or a combination of these symptoms were calculated using Chi Square tests for dichotomous and ordinal variables and a one way ANOVA between subjects for continuous variables. Friedman's tests were used to calculate an overall difference in symptom report between the preoperative and the six months measurement. Changes in symptom report across time were investigated using Wilcoxon Signed Rank tests (for ordinal variables) and McNemar tests (for dichotomous variables). Significance was obtained from Chi Square tests and Binominal Tests if necessary.

Persistence and emergence rates were obtained for 'any symptom'. Persistence was defined as patients reporting the same symptom preoperatively and at six months. An overall score was calculated for biliary, dyspeptic, and biliary/dyspeptic symptoms. Emergence was defined as patients who did not report a symptom preoperatively, but who *did* report that symptom at six months. Again an overall score was obtained for biliary, dyspeptic, and biliary/dyspeptic symptoms.

Univariate logistic and multinominal regression analyses, taking 'symptom free' as reference group, were performed to identify predictors of postoperative symptoms at six months. These analyses were used for dichotomous and categorial outcomes, respectively. Significant predictors were selected and inserted in multivariate logistic or multinominal regression analysis (Backward procedure, Method Likelihood Ratio) to identify independent predictors of postoperative symptom report. 'Symptom free' was used as reference category in multinominal regression analyses. A p value < .05

indicated statistical significance. Statistical analyses were performed using SPSS version 16.0.

Figure 1. Flow chart of the population under study.



Results

A flow-chart of the population under study is shown in figure 1. In total, 253 patients received the first set of questionnaires, of which 172 patients returned their questionnaires at six months after cholecystectomy (response rate 68.0%). Clinical and demographic patient characteristics are shown in table 1. The majority of patients (61.9%) reported both biliary and dyspeptic symptoms (Table 2). Moreover, 24.5% of the patients only reported biliary symptoms, and 13.6% of the patients only reported dyspeptic symptoms. In this study, groups of patients were based on the report of

preoperative biliary symptoms (group 1), dyspeptic symptoms (group 2), or both (group 3). These groups did not differ on any clinical or demographic characteristics.

Table 1. Demographic and clinical characteristics (n = 172).

Demographic characteristics	
Female patients (%)	76.2
Age (M ± SD)	47.51 ± 11.33
Highest level of education	
Primary or lower vocational education (%)	17.1
Secondary education (%)	49.4
Higher education (%)	6.4
Higher professional education or university (%)	27.1
Working under payment (%)	68.8
Marital status	
Single (%)	4.1
Widowed or divorced (%)	5.9
Married or cohabitant (%)	90.0
Medical characteristics	
Self-reported medication use	
Analgesics (%)	36.8
Psychotropic medication (%)	9.9
Other medication (%)	49.7
Comorbidities	
Coronary arterial disease (%)	18.0
Pneumonal disease (%)	5.8
Abdominal disease (%)	22.1
Kidney diseases (%)	0.6
Urogenital diseases (%)	8.1
Neurological diseases (%)	9.9
Other comorbidities (%)	43.6
High trait anxiety (HTA) STAI-Trait ≥ P 80 (%)	20.1

Six months benefit of cholecystectomy

At six months after the operation, the majority of patients had started their normal daily activities (95.5%). Of the patients who had paid work (n = 117), 99.1% had returned to work, whereas 0.9% of the patients had not returned to work. At six months, a substantial group of patients still reported specific postoperative health complaints, such as wound pain (7.2%), shoulder pain (10.1%), and pain in the upper right abdomen

(13.7%). Six months after cholecystectomy, 47.8% of the patients were free of symptoms (see figure 2), whereas persistence and emergence of any symptom was reported by 17.9% and 34.0% the patients, respectively. Over six months time, the number of patients with biliary symptoms only and a combination of biliary and dyspeptic symptoms decreased from 24.5% to 3.1% and from 61.9% to 14.3%, respectively. However, the number of patients that reported dyspeptic symptoms increased from 13.6% preoperatively to 34.8% at six months postoperatively (see figure 2).

Patient groups were compared with regard to postoperative symptomatic outcome at six months. Regardless of specific outcomes, the overall symptomatic outcome of patients in group 2 differed significantly from the outcome of the other patient groups ($\chi^2 = 8.30$, $p = .040$). At six months, the three patient groups differed significantly with regard to the report of any postoperative symptom (biliary or dyspeptic) ($\chi^2 = 6.29$, $p = .043$). Postoperative symptoms were reported by 68.4% of the patients in group 2, whereas postoperative symptoms were reported by 37.5% and 60.2% of the patients in group 1 and 3, respectively. Group 3 ($n = 53$) differed significantly from the other two groups.

Furthermore, the groups differed significantly with respect to the persistence of the same pattern of preoperative symptoms ($\chi^2 = 25.02$, $p < .001$). Pre-existing symptoms persisted most often in group 2 (63.2%), followed by patients in group 3 and group 1 (18.2% and 3.1% of the patients, respectively). Furthermore, preoperative groups differed significantly regarding the development of new symptoms postoperatively ($\chi^2 = 11.64$, $p = .003$). Six months after cholecystectomy, patients in group 2 less often developed symptoms from another category than patient in the other groups (5.3% vs. 37.8% ($\chi^2 = 6.52$, $p = .011$)). Patients in group 3 were most likely to develop symptoms of another category, compared to patients in the other groups (42.0% vs. 24.3% ($\chi^2 = 4.87$, $p = .027$)). In fact, 4.5% and 37.5% of all patients in group 3, reported only postoperative biliary or only postoperative dyspeptic symptoms, respectively. This implicates that preoperative biliary symptoms subsided more often. Preoperative groups did not differ with regard to the report of postoperative non-specific symptoms.

Figure 3 gives an overview of postoperative symptoms at six months for each group. Within each group, the number of patients reporting the prominent preoperative symptom decreased. In group 1, a significant number of patients developed a different pattern of complaints with dyspeptic symptoms only ($p = .005$). Furthermore, over six months time, the number of patients with non-specific symptoms decreased within

group 1 (p = .002) (figure 4). In contrast, in group 2 the number of patients with non-specific symptoms did not decrease. In group 3, a decrease of patients with non-specific symptoms (p < .001) and a change to individual biliary (p = .046) or dyspeptic symptoms (p < .001) was observed at six months.

Table 2. Preoperative presentation of cholelithiasis.

Preoperative symptom report	
Upper abdominal pain (%)	66.5
Nausea (%)	40.4
Vomiting (%)	56.1
Bad taste(%)	21.6
Heartburn (%)	27.5
Under abdominal pain (%)	20.5
Diarrhoea (%)	18.7
Flatulence (%)	36.8
Biliary symptoms[†] only (%)	24.5
Dyspeptic symptoms[§] only (%)	13.6
Biliary[†] and dyspeptic[§] symptoms (%)	61.9
Demonstrated stones or sludge (%)	91.9
Preoperative biliary attacks (M ± SD)	5.2 ± 7.2
Pain during biliary attack	
Pain in rest and movement (%)	94.3
Pain only in rest (%)	4.5
Pain only in movement (%)	1.2
Non-specific symptoms*(%)	56.1

[†] Biliary symptoms = one or more of the following symptoms: upper abdominal pain, nausea, and vomiting.

[§] Dyspeptic symptoms = one or more of the following symptoms: bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence.

*Non-specific symptoms = one or more of the following symptoms: general malaise (9.4%), fatigue (49.7%), weight change (2.9%), decreased sexual functioning (10.5%), and other health complaints (12.3%).

Figure 2. Report of symptoms preoperatively and at six months post-cholecystectomy.

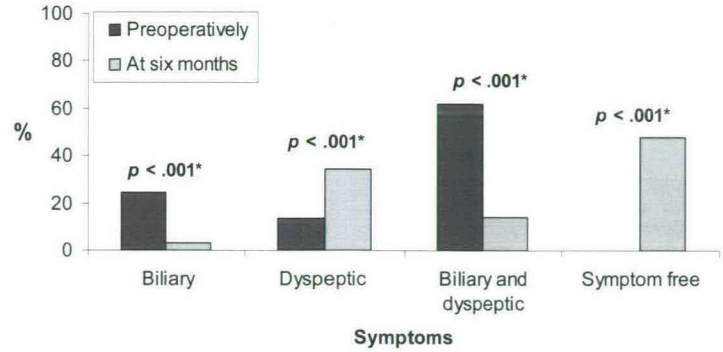


Figure 3. Report of symptoms at six months post-cholecystectomy.

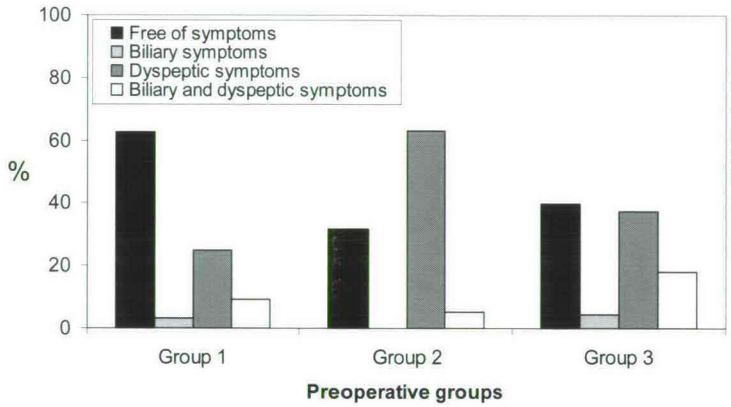
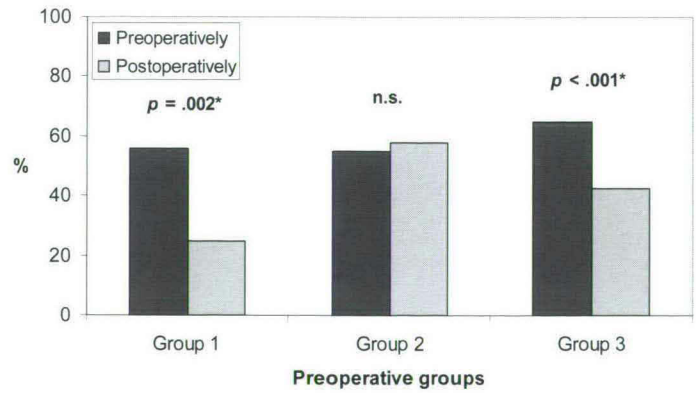


Figure 4. Report of non-specific symptoms at six months post-cholecystectomy.



Predictors of six months outcome

Univariate logistic regression analyses were performed to identify predictors of the report of (any) symptoms at six months. These results are shown in table 3. Multivariate regression analyses demonstrated that the postoperative report of biliary and/or dyspeptic symptoms was predicted by preoperative non-specific symptoms only (*OR* = 3.06, *p* = .003; 95% *CI*: 1.46 – 6.42). When groups of patients were investigated separately, preoperative non-specific symptoms were the only predictor of any postoperative symptom in group 1 (*OR* = 6.11, *p* = .043; 95% *CI*: 1.06 – 35.35) and group 2 (*OR* = 4.53, *p* = .002; 95% *CI*: 1.77 – 11.60). No predictors were identified for the report of any postoperative symptom in group 3.

Predictors of persistence of existing symptoms were investigated by univariate logistic regression analyses (see Table 4). Multivariate logistic regression analysis demonstrated that the use of psychotropic medication (*OR* = 5.27, *p* = .010; 95% *CI*: 1.50 – 18.55) and the preoperative report of dyspeptic symptoms only (*OR* = 16.69, *p* < .001; 95% *CI*: 4.59 – 60.68) were independent predictors of persisting symptoms. Univariate and multinominal regression analyses were performed to identify predictors of postoperative biliary symptoms, dyspeptic symptoms and a combination of biliary and dyspeptic symptoms. Results of univariate regression analyses are shown in table 5. Entering these predictors simultaneously in a multivariate multinominal regression analysis demonstrated that postoperative biliary symptoms were predicted by HTA only, whereas postoperative dyspeptic symptoms were independently predicted by preoperative dyspeptic and non-specific symptoms. Furthermore, non-specific symptoms and the use of psychotropic medication predicted a postoperative course with both biliary and dyspeptic symptoms (see Table 6).

Table 3. Univariate predictors of symptom report (biliary and/or dyspeptic) at six months after cholecystectomy.

Preoperative characteristic	***OR***	***95% CI***	***p***
Psychotropic medication	3.44	1.07–11.04	.038*
Non-specific symptoms	2.85	1.49 – 5.45	.002*
Combination of biliary and dyspeptic symptoms	2.10	1.12 – 3.94	.021*
HTA	2.89	1.23 – 6.79	.015*
Neurologic comorbidity	4.17	1.13–15.38	.032*

* $p < .050$ indicated significance. Significant results are reported only.

Table 4. Univariate predictors of persistence of preoperative symptoms.

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Persistence of preoperative symptoms	Dyspeptic symptoms only	12.71	4.40 – 36.70	<.001*
	HTA	2.89	1.16 – 7.18	.023*
	Number of non-specific symp.	1.50	1.02 – 2.20	.041*
	Psychotropic medication	5.51	1.90 – 15.96	.002*
	Abdominal comorbidity	2.78	1.16 – 6.63	.022*

* $p < .050$ indicated significance. Significant results are reported only.

Table 5. Univariate predictors of postoperative symptoms (category yes/no).

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Biliary symptoms only	HTA	12.19	1.76 – 84.30	.011*
Dyspeptic symptoms only	Dyspeptic symptoms only	3.23	1.13 – 9.22	.029*
	Neurologic comorbidity	4.72	1.22 – 18.35	.025*
	Non-specific symptoms	2.11	1.04 – 4.26	.038*
Biliary and dyspeptic symptoms	Use of psychotropic medication	9.73	2.59 – 36.53	.001*
	HTA	5.00	1.59 – 15.74	.006*
	Biliary and dyspeptic symptoms	2.74	1.01 – 7.42	.047*
	Non-specific symptoms	8.01	2.19 – 29.33	.002*

* $p < .050$ indicated significance. Significant results are reported only.

Table 6. Independent predictors of postoperative symptoms (based on multivariate multinominal regression analyses).

Postoperative outcome	Preoperative predictor	*OR*	95% *CI*	*p*
Biliary symptoms	HTA	10.64	1.24 – 90.96	.031*
Dyspeptic symptoms	Dyspeptic symptoms only	5.69	1.50 – 21.63	.011*
	Non-specific symptoms	2.50	1.10 – 5.64	.028*
Biliary and dyspeptic symptoms	Non-specific symptoms	9.53	1.86 – 48.92	.007*
	Use of psychotropic medication	8.01	1.75 – 36.75	.007*

* $p < .050$ indicated significance. Significant results are reported only.

Discussion

The results of cholecystectomy can be disappointing for many patients. Currently, the indication of an elective cholecystectomy is such that many patients are operated without critical consideration of individual expectations and risks. At six months after cholecystectomy, only 47.8% of the patients were symptom free. In addition, 17.9% and 34.0% of the patients reported persistence and emergence of new symptoms, respectively. As it concerns a substantial numbers of patients, preoperative recognition of patients with an increased risk of negative outcomes is essential to optimise the management of cholelithiasis. The present study demonstrated that patients with preoperative dyspeptic symptoms and patients using psychotropic medication are both at risk of persistence of the pre-existing pattern of health complaints after cholecystectomy. Furthermore, patients with non-specific symptoms and patients using psychotropic medication are at risk of the experience of biliary and/or dyspeptic symptoms at six months. Patients with High Trait Anxiety have a ten times greater chance to experience specifically postoperative biliary symptoms.

The current study investigated six month outcomes, as the greatest improvement after cholecystectomy is seen within this time period[23]. Overall, comparability of studies focussing at approximately six months is limited[10, 13, 15, 24], because of differences in criteria for inclusion, designs, classification, definition and operationalisation of outcomes, and variability in moments of follow-up. The percentage of patients who are free of symptoms or report persisting symptoms is comparable to results of other studies focussing at six months[10, 13, 15]. The percentage of patients who develop new symptoms (34.0%) is higher than those percentages found in other studies (1.7% – 24.5%)[10, 13, 15, 24]. This may be attributed to patients in group 3 who recover partially and report only biliary or dyspeptic symptoms after cholecystectomy.

In the current study, dyspeptic symptoms persisted more often than biliary symptoms, which is in line with other studies focussing at six months after cholecystectomy[13, 24]. Differentiation between patient groups showed that patients with only dyspeptic symptoms have the worst prognosis: dyspeptic symptoms often tended to persist (63.2%) over six months time. In patients with a combined symptom profile dyspeptic symptoms tend to persist[15] and dyspeptic symptoms developed in 25% of the patients with preoperative biliary symptoms. The latter findings support a shift towards dyspeptic symptomatology at six months, as mentioned in previous studies[13, 15]. This

shift may be related to pre-existent gastrointestinal symptoms[24], postoperative changes in duodenogastric reflux[24], retained stones, the formation of new gallstones[25], or the impact of psychological variables such as HTA.

We found that patients with preoperative non-specific symptoms are also at risk for any postoperative dyspeptic or combined dyspeptic and biliary symptoms. The cause of these non-specific symptoms is unclear. Non-specific symptoms may coincide with biliary, dyspeptic or other symptoms, or comorbid conditions. Otherwise, non-specific symptoms may contain a more subjective component and may be influenced by psychological variables, such as depressive symptoms or personality. Weinert et al.[13] demonstrated that a subjective measure, namely self-rated preoperative health status (SF-36) predicts outcomes at six months after cholecystectomy. However, the SF-36 contains some general items such as bodily pain, which could also be related to biliary and dyspeptic symptoms. Therefore, we believe that a parsimonious list of non-specific symptoms may be more precise and better differentiates general symptoms from pure biliary and dyspeptic symptoms. Although preliminary results suggest that patients with non-specific symptoms are at risk of negative post-cholecystectomy outcomes, further research needs to corroborate this finding and to address the issue of subjectivity.

As persistent biliary symptoms are decisive for the subjective perception of a successful procedure[13], special attention needs to be paid to patients with HTA, who are at risk to report persisting biliary symptoms at six months post-cholecystectomy. So far, HTA has been identified as a potential predictor of short-term post-cholecystectomy outcomes only[26, 27]. Patients with HTA are predisposed to react with heightened anxiety to threatening situations[28], and may misinterpret a broad range of gastrointestinal symptoms as being of biliary nature. Misinterpretations may be mediated by the fact that HTA patients have higher pain sensitivity[29] and experience more gastrointestinal symptoms than other patients[30]. Because of these characteristics, HTA patients may be easily misdiagnosed as suffering from cholelithiasis and abusively be subjected to cholecystectomy. Consequently these patients will report persistence of pre-existing symptoms. Possibly, psychosomatic mechanisms typically for HTA patients, such as heightened activity of the sympathetic nervous system[31] and production of higher levels of noradrenaline[32], may influence digestion, wound healing or other bodily processes, which could be related to the experience of pain after removal of the gallbladder. The role of HTA on long-term post-cholecystectomy outcomes and underlying mechanisms should be further corroborated in future research.

The present study has several strengths, such as the prospective design and the participation of consecutive patients, which prevents a selection bias. In contrast to other studies[10, 13, 15, 24], we used strict criteria for inclusion of patients, such as symptomatic cholelithiasis, ASA I and II, limited age differences, indicated for elective cholecystectomy only, and used a big sample size (n = 172). Follow-up was limited to the period of 6 to 9 months postoperatively. These conditions create a homogenous sample, which enables strong conclusions which are applicable to the field of action where critical consideration matters most: elective surgery. Another advantage of the study is the fact that clinical presentation of preoperative symptoms was used as a basis for further investigation of predictors. This enlarges the specificity of the predictors for cholelithiasis and enables the clinical application of the results. The fact that we dichotomised many variables (yes/no) enhances the convenience to apply our findings in surgical practice. On the other hand, it entails the risk of oversimplification of our conclusions.

Other limitations of the study are the fact that we used a self-constructed symptom checklist, instead of a standardised gastrointestinal questionnaire. We found it legitimate to use such a checklist, because we carefully based our symptom checklist on information from focus groups, other symptom checklists, and clinical experience. Currently no disease specific symptom checklist exists for cholelithiasis. The fact that we used broad symptom categories, according to a leading article of Weinert et al.[13], increased the comparability to this study in particular. However, as categorising symptoms into biliary or dyspeptic symptoms is highly arbitrarily, comparability with other studies might be hampered. Given the ambiguous clinical presentation of cholelithiasis and the vague diagnostic criteria, classification of symptoms as being purely biliary or dyspeptic in nature seems to be extremely difficult. Furthermore, this study has the disadvantage that we have two separate measures, at baseline and at follow-up at six months. Therefore the study does not differentiate between the persistence of symptoms and the development of symptoms after initial disappearance after cholecystectomy. Comparing findings shortly after cholecystectomy (e.g. six weeks) with findings at six months may convey the course of symptoms over time. Finally, in the current study we did not control for confounding postoperative variables, such as comorbid diseases and major life events. Therefore, results at six months may be influenced by other factors than the recovery after cholecystectomy.

Implications

The results of the present study may have implications for the management of symptomatic cholelithiasis. Surgeons should be aware that less than half of their patients are free of symptoms at six months after cholecystectomy. Patients should be informed about the considerable risk of persistent and developing symptoms at six months. Generally, cholecystectomy is used to prevent further episodes of biliary colics and complications[8], whereas expectative management is often disregarded. The use of ursodeoxycholic acids (in combination with lithotripsy) remains a matter of debate[33]. If treated expectatively, the risk of complications such as acute cholecystitis, acute pancreatitis, or biliary duct obstruction is small (1% – 2% a year)[34, 35] and biliary pain recurs only in 31% of the patients with previous biliary attacks > 1 year[36]. Most interesting is that over a period of five years, pain reduction, the rate of complications, and improvements of quality of life (QoL) are equal for expectative management and cholecystectomy. Starting expectatively, only 23% – 49% of the patients underwent cholecystectomy because of recurred pain and complications within 2.5 – 5 years[23, 37]. As expectative management is safe and offers a good prospective in cholelithiasis, it should be a preferred treatment to start with in patients with a high risk of postoperative symptoms.

Recognition of high risk patients is crucial to gear the treatment to the patient's characteristics. In patients with classical biliary symptoms (alone or together with dyspeptic symptoms), surgeons should be attentive to non-specific symptoms during anamnesis. In patients using psychotropic medication and patients reporting dyspeptic symptoms only, wait-and-see should be considered as the treatment of choice. Limiting our recommendations to the persistence of biliary symptoms, which are most indicative of a successful procedure, patients with HTA should be treated alternatively or at least be informed about their heightened risk. Alternatively, psychotherapeutic interventions stemming from cognitive behavioural therapy or mindfulness may teach patients how to deal with anxiety provoking situations and may reduce stress in HTA patients. Consequently, the negative influence of HTA may be reduced and postoperative symptomatic outcomes may be improved. Summarised, in cholelithiasis surgeons should offer patients a treatment which is based on individual risks and expectations. Hopefully, the rate of unsuccessful treatments will be reduced, which will lead to greater cost-efficiency in health care.

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Chapter 6

Clinical decision making in cholecystectomy: Do preoperative symptoms matter?

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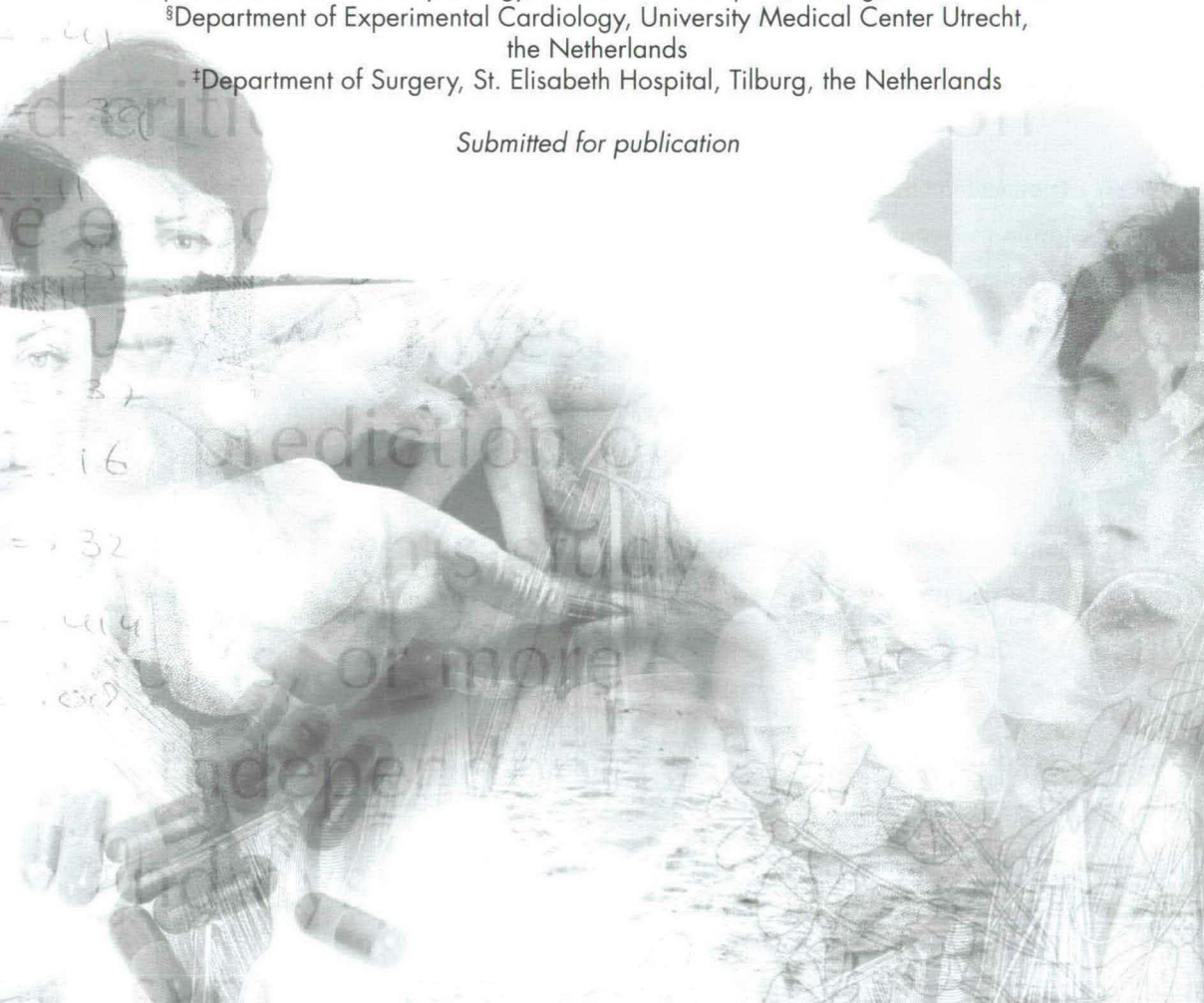


Abstract

Background: Many patients report persisting symptoms after cholecystectomy. The aim of this study is to examine symptomatic outcome and overall QoL one year after cholecystectomy and to identify predictors for these outcomes.

Method: This prospective follow-up study was conducted in a teaching hospital in the Netherlands. Consecutive patients (n = 156), age 18 – 65 yrs, diagnosed with uncomplicated symptomatic gallstone disease, awaiting an elective cholecystectomy, were included in this the study. Cholecystectomy was performed under a standard anaesthetic regime. Predictors of symptomatic outcome (i.e. 'free of symptoms', 'biliary symptoms only', 'dyspeptic symptoms only', and 'biliary and dyspeptic symptoms') and QoL were investigated one year after cholecystectomy.

Results: Patients with different preoperative symptoms (biliary symptoms, dyspeptic symptoms or a combination of both) showed different symptomatic improvements one year after cholecystectomy. Preoperative non-specific symptoms predicted the report of biliary and dyspeptic symptoms at one year (*OR* = 2.63, 95% *CI*: 1.03 – 6.70). In the course of one year, overall QoL improved in patients with biliary symptoms only and a combination of biliary and dyspeptic symptoms. Patients with dyspeptic symptoms only showed no improvement in overall QoL. Overall QoL at one year is predicted by the preoperative clinical picture (β = - .24), abdominal comorbidity (β = - .33) and high trait anxiety (β = - .43).

Conclusions: The clinical presentation of gallstone disease has an impact on symptomatic outcome and overall QoL at one year. Preoperative symptoms and other risk factors of low improvements in symptoms and overall QoL should be considered, to aim at an optimal treatment for each patient. Clinical decision making in gallstone disease should focus on improvements in overall QoL instead of symptoms.

Introduction

In the Western world up to 22% of all individuals suffer from gallstone disease (cholelithiasis)[1-3]. A relatively small percentage of these patients (10 – 30%) develop clinical significant symptoms, varying from classical biliary colics to a chronic pattern of dyspeptic symptoms, in which case removal of the gallbladder (cholecystectomy) is indicated[4-7]. Guidelines recommend the use of additional ultrasonography to detect gallstones. However, it often remains uncertain whether abdominal pain is purely related to demonstrated gallstones. Nevertheless, cholecystectomy is the golden standard and thus the most frequently used treatment. Alternative treatment options or conservative management are considered in high-risk surgical patients only.

Many patients, percentages mount from 13% to 44% of all patients[8-13], report persisting symptoms and pain regardless of treatment. Research has identified several risk factors of negative outcomes. Clinical characteristics, more specifically dyspeptic symptoms[14-16] and preoperative pain[14, 16-18], preoperative medication use[9], and age[18] are associated with short- and long term outcomes after cholecystectomy. In the realm of psychological characteristics, self-rated health status[14], personality traits[16, 19], and other psychological variables[10, 19, 20] are considered to have an impact on post-cholecystectomy outcomes. However, these predictors have not found their way to clinical practice and seldom lead to changes in decision making. So far, Quality of Life (QoL), which is a subjective measure, has not been investigated as an outcome after cholecystectomy. Predictors of post-cholecystectomy QoL are unknown.

The purpose of the present study was to investigate symptomatic outcome and overall QoL at one year after cholecystectomy, taking the clinical picture of gallstone disease as a starting point. Another aim of the study was to identify predictors of symptomatic outcome and overall QoL at one year after cholecystectomy.

Methods

Patients

Patients were recruited from the Department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Consecutive patients (18 – 65 years) with diagnosed symptomatic cholelithiasis, visiting the hospital between March 2006 and January 2008, who awaited an elective laparoscopic cholecystectomy, were eligible for the study.

Exclusion criteria were: patients with ASA class III or IV, undergoing an emergency procedure or intended open cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases. All patients underwent a standard surgical and anaesthetic procedure. The protocol of the study was approved by the local ethics committee.

Procedure

Preoperatively, participation was asked during the patients' first surgical consultation at the outpatient clinic. The surgeon introduced the study, whereas subsequently nurses informed patients about the research procedures. Patients received the first set of questionnaires, which also contained written information about the study, and signed informed consent. Medical history and comorbidities were obtained from medical records. Patients completed and returned the first questionnaires before admission for cholecystectomy. If necessary, patients received a reminder telephone call to return the questionnaires three to five days before the operation. Patients who returned the questionnaires after admission were excluded from the study. At six months after cholecystectomy, patients received the same questionnaire which could be returned in a prepaid envelope. If needed, patients were contacted by telephone twice, usually two and four weeks after sending the questionnaires. Patients returning their second questionnaire > 15 months after surgery were considered as non-responders.

Questionnaires

The demographic questionnaire was completed preoperatively and asked about sex, age, marital status, educational level, and work. Preoperatively and at one year after cholecystectomy, patients completed a symptom checklist based on information from focus groups, literature and clinical experience. Patients should tick off whether they experienced biliary symptoms (upper abdominal pain, nausea, vomiting), dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea, and flatulence), and non-specific symptoms (general malaise, fatigue, weight-change, decrease in sexual functioning, and health complaints not mentioned in the pre-defined checklist) in the past week. Symptoms were categorised following the study of Weinert et al.[14]. All included patients had experienced biliary or dyspeptic symptoms in medical history.

Preoperatively and at one year, patients reported medication use by indicating the dosis and name of medications.

Patients completed the trait scale of the State-Trait Anxiety Inventory (STAI) preoperatively. The STAI-trait exists of 20 items with a 4-item Likert-scale reflecting the extent of anxiety patients generally feel. The STAI Trait Anxiety measure has good 3 months test-retest reliability (r = .75) and internal consistency (Cronbach's α = .84 – .92)[21]. Patients scoring the 80th percentile or higher were indicated as patients with 'High Trait Anxiety' (HTA), whereas patients with a score below the 80th percentile were indicated as patients with 'Non High Trait Anxiety' (NHTA).

Preoperatively and at one year patients completed the World Health Organization Quality of Life (WHOQOL)-BREF, which has been developed from the WHO definition of QoL as ' an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectation, standards and concerns'[22]. The WHOQOL-BREF has adequate to moderate internal consistency (Cronbach's α = .68 – .80) and adequate test-retest reliability (r = .71 – .91)[23, 24]. The WHOQOL-BREF originally comprises 26 items with a 5-point Likert-scale, representing different domains of the patient's quality of life (QoL). Two items referring to overall QoL and general health were used in this study[25].

Statistical procedures

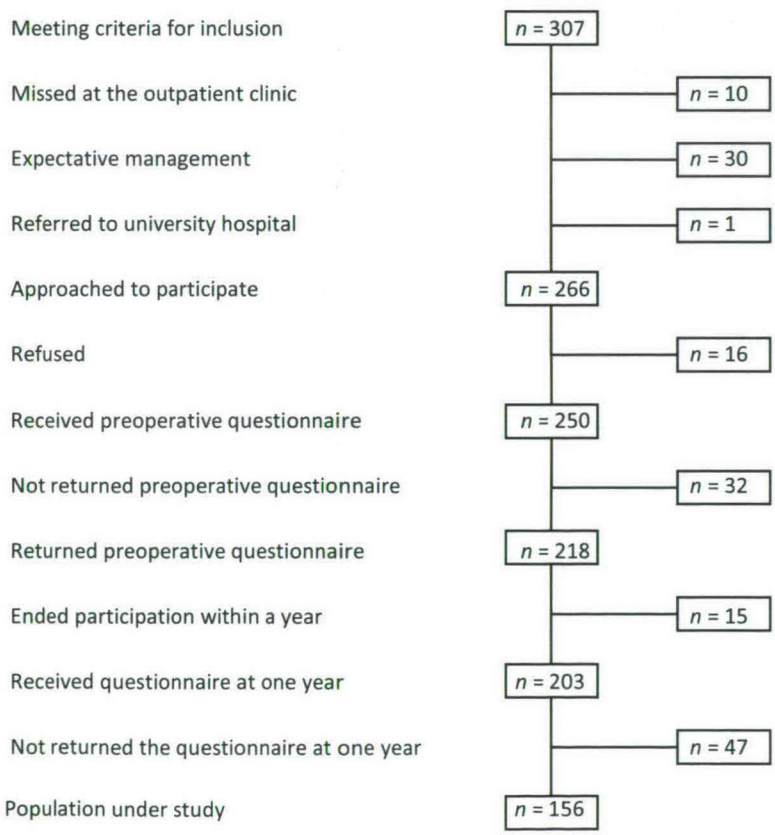
Differences between participants and non-participants were investigated using Chi square tests (with Yates' Continuity Correction and Fisher Exact Test if necessary) and Students t-tests. Patients with different preoperative characteristics were categorized in three groups. Pre- and postoperative outcomes were investigated separately for patients with preoperative biliary symptoms only (group 1), preoperative dyspeptic symptoms only (group 2), and preoperative biliary *and* dyspeptic symptoms (group 3). Pre- and postoperative differences between the groups were initially investigated by Kruskal-Wallis tests and one-way independent ANOVA's (post-hoc tests using Tuckey HSD tests and planned comparisons if possible). Paired samples t-tests and Wilcoxon Signed Ranks Tests were used to calculate changes over time for continuous and categorical variables, respectively. Repeated measure ANOVA was used to examine changes in the number of symptoms in the course of one year.

Univariate and multivariate logistic regression analyses were performed to identify predictors of several outcomes at one year, namely 'free of symptoms', 'only biliary

symptoms', 'only dyspeptic symptoms', 'biliary *and* dyspeptic symptoms', and QoL. Sex, age, medication use, frequency of biliary attacks, pain during biliary attacks, non-specific symptoms, HTA, and preoperative patient groups were investigated as univariate predictors of one year symptomatic outcomes after cholecystectomy. To optimize clinical application, preoperative patient groups were inserted as dichotomous items (yes/no). Significant univariate predictors were entered simultaneously in multivariate logistic regression analyses (Method enter). If two overlapping items, such as presence and number of symptoms, were both significant univariate predictors, the dichotomous item was selected as predictor in the multivariate regression analyses. To facilitate interpretation, outcome variables were recoded if odds ratios were < 1.0.

Univariate linear regression was used to identify possible predictors of overall QoL and general health at one year. Independent predictors of overall QoL at one year after cholecystectomy were identified using multiple regression (Method Enter).

Figure 1. Flow chart of the population under study.



Results

Preoperative symptoms

Preoperatively, 266 patients were approached for study, of which 250 patients received the first questionnaire. At one year follow-up, 156 participants completed the questionnaire (response rate 62.4%). A flow chart of the population is shown in figure 1. The only difference between patients that ended participation or did not return the second questionnaire and participants concerned biliary attacks. Participants reported more preoperative biliary attacks (6.07 ± 8.53 vs. 3.75 ± 3.70; $t = 2.65$, $p = .009$), than non-responders and patients that ended participation. Demographic and clinical characteristics of the sample are shown in table 1.

Preoperatively all patients reported symptoms: 24.3% reported biliary symptoms only (group1), 14.7% reported dyspeptic symptoms only (group 2), and 61.0% of the patients biliary and dyspeptic symptoms (group 3) (see Table 2). HTA was represented equally in the three groups. The patient groups differed with respect to the number of preoperative non-specific symptoms reported ($F = 5.45$, $p = .005$). Patients in group 3 reported most non-specific symptoms ($p = .006$), whereas patients in group 1 reported fewest non-specific symptoms ($p = .039$). Preoperatively, patient groups did not differ with respect to overall QoL and general health ($F = 2.76$, $p = .067$).

Postoperative symptoms

Postoperative outcomes for the sample are shown in table 2. Overall, 50.0% of all patients were free of symptoms at one year after cholecystectomy. At one year the three groups differed with respect to the report of heartburn (Kruskal Wallis $\chi^2 = 6.64$, $p = .036$) and the number of biliary symptoms ($F = 5.45$, $p = .005$). With regard to broad symptomatic outcomes, in comparison with the other two patient groups, patients in group 1 were most often relieved of symptoms at one year (66.7% vs. 44.7%, $\chi^2 = 4.00$, $p = .045$), whereas patients in group 2 were most likely to report only dyspeptic symptoms one year after cholecystectomy (72.7% vs. 38.6%; $\chi^2 = 3.08$, $p = .050$). In addition, patients in group 1 reported less non-specific symptoms than patients in the other groups ($p = .006$), whereas patients in group 2 reported less biliary symptoms than patients in the other groups ($p = .018$). At one year, patients in group 3 reported a greater number of biliary and non specific symptoms than the other patients did (($p = .012$) and ($p = .012$), respectively). At one year after cholecystectomy, medication

use had not changed for patients in groups 1 and 2, whereas the use of other than analgesic and psychiatric medication has increased significantly in group 3 (Z = - 3.21, p = .001).

One year after cholecystectomy overall QoL and general health differed between the patient groups (F = 4.75, p = .010). Patients in group 1 reported higher overall QoL than patients in group 2 and 3 ((p = .046) and (p = .012), respectively). Postoperative QoL did not differ between patients in group 2 and 3 (p = .951).

Table 1. Demographic and clinical characteristics (n = 155).

Demographic characteristics	
Female patients (%)	75.6
Age (M ± SD)	46.88 ± 11.98
Highest level of education	
Primary or lower vocational education (%)	16.2
Secondary education (%)	51.3
Higher education (%)	6.5
Higher professional education or university (%)	26.0
Working under payment (%)	70.1
Marital status	
Single (%)	3.9
Widowed or divorced (%)	5.2
Married or cohabitant (%)	90.8
Comorbidities	
Coronary arterial disease (%)	20.4
Pneumonal disease (%)	5.3
Abdominal disease (%)	26.5
Kidney diseases (%)	0.9
Urogenital diseases (%)	8.0
Neurological diseases (%)	10.6
Other comorbidities (%)	49.6
High Trait Anxiety (HTA) STAI-Trait ≥ P 80 (%)	21.8

Table 2. Pre- and postoperative disease-specific characteristics.

Disease-specific characteristics	**Preoperatively**	**Postoperatively**	***Z***	***p***
Free of symptoms (%)	0.0	50.0	-8.25	<.001*
Biliary symptoms only (%)	24.3	8.3	-.47	.67
Upper abdominal pain (%)	68.8	21.2	-8.27	<.001*
Nausea (%)	40.0	9.0	-6.20	<.001*
Vomiting (%)	18.1	2.6	-4.24	<.001*
Dyspeptic symptoms only (%)	14.7	25.0	-3.80	<.001*
Bad taste (%)	19.4	7.1	-3.41	.001*
Heartburn (%)	26.5	16.7	-2.53	.011*
Under abdominal pain (%)	20.0	12.2	-1.95	.052
Diarrhoea (%)	18.7	10.3	-2.34	.020*
Flatulence (%)	36.8	22.6	-2.78	.005*
Combination of biliary and dyspeptic symptoms (%)	61.0	16.7	-3.77	<.001*
Non-specific symptoms[‡] (%)	61.0	33.0	-4.59	<.001*
Self-reported medication use				
Analgesics (%)	34.8	30.4	-1.88	.061
Psychotropic medication (%)	9.7	17.9	.00	1.00
Other medication (%)	49.7	85.1	4.59	<.001*

	M ± SD	M ± SD	*t*	*p*
Number of symptoms reported				
Number of biliary symptoms	1.27 ± .97	.32 ± .64	10.70	<.001*
Number of dyspeptic symptoms	1.20 ± 1.14	.69 ± .98	4.52	<.001*
Number of non-specific symptoms	.86 ± .96	.48 ± .81	4.13	<.001*
General QoL and general health	7.21 ± 1.69	7.78 ± 1.64	-4.35	<.001*

[‡]Non specific symptoms = one or more of the following symptoms general malaise, fatigue, weight change, decreased sexual functioning, and other health complaints.

* $p < .050$ indicated statistical significance.

Benefit from cholecystectomy at one year

Overall, patients benefited from cholecystectomy in terms of a significant decrease of symptoms (see Table 2). In the course of one year after cholecystectomy, the use of analgesics and psychotropic medication did not change, whereas the use of other medication increased significantly. Differential benefits for patients within the preoperative patient groups are shown in table 3.

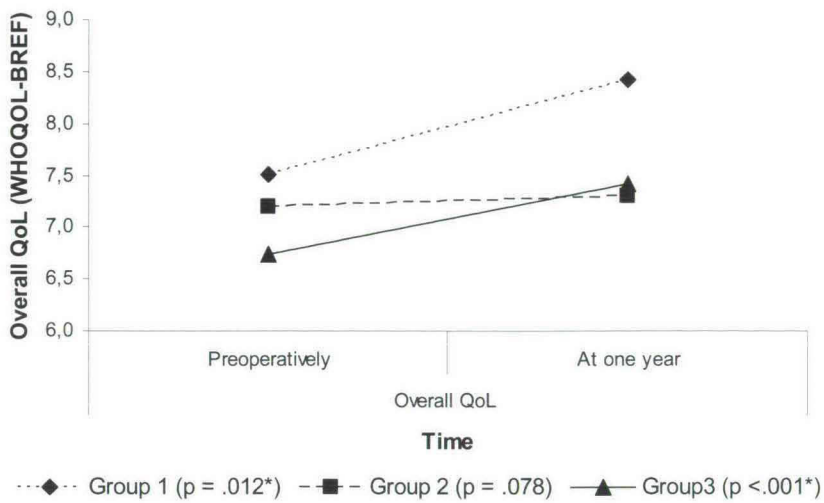
Changes in overall QoL and general health over time for different patient groups are shown in figure 2. Patients in group 1 and group 3 reported an improvement of overall QoL ($F = 7.20$, $p = .012$; $\varepsilon^2 = .19$) and ($F = 13.52$, $p < .001$; $\varepsilon^2 = .14$). Patients in group 2 did not report an increase in QoL ($p = .078$). With respect to QoL, repeated measure ANOVA demonstrated a main effect for time ($F = 9.40$, $p = .003$; $\varepsilon^2 = .07$) and preoperative category ($F = 5.14$, $p = .007$; $\varepsilon^2 = .07$), but no interaction effect for time * preoperative category ($p = .31$). Overall QoL and general health changed over one year time and differed between patients in different groups. However, the observed changes in QoL over time were equal for the different patients groups.

Table 3. Changes in symptom report in the course of one year after cholecystectomy.

	Group 1			Group 2			Group 3	
	Z	*p*		*Z*	*p*		*Z*	*p*
Biliary symptoms								
Upper abdominal pain	• **-5.20**	**<.001***	-	1.00	.317	•	**-6.86**	**<.001***
Nausea	• **-3.46**	**.001***	-	.00	1.000	•	**-5.31**	**<.001***
Vomiting	- -1.89	.059	-	.00	1.000	•	**-3.80**	**<.001***
Dyspeptic symptoms								
Bad taste	- 1.00	.317	•	**-2.00**	**.046***	•	**-3.40**	**.001***
Heart burn	- 1.00	.317	-	-1.41	.157	•	**-2.87**	**.004***
Under abdominal pain	- 1.73	.083	-	-1.27	.206	•	**-2.71**	**.007***
Diarrhoea	- 1.41	.157	-	-1.34	.180	•	**-2.96**	**.003***
Flatulence	□ **2.65**	**.008***	•	**-2.11**	**.035***	•	**-4.23**	**<.001***
Non-specific symptoms	• **-2.89**	**.004***	-	-1.51	.132	•	**-3.55**	**<.001***

• decrease of symptoms □ emergence of symptoms
- no change * $p < 0.050$ indicated statistical significance

Figure 2. Changes in overall QoL and general health at one year after cholecystectomy.



Prediction of postoperative outcomes

Table 4 shows univariate predictors of the postoperative outcomes 'free of symptoms', 'biliary symptoms only', 'dyspeptic symptoms only', 'biliary and dyspeptic symptoms'. No univariate predictors could be identified for the outcome of both biliary and dyspeptic symptoms at one year. The univariate predictors were simultaneously entered for each postoperative outcome. Since the variables 'non specific symptoms' (yes/no) and 'number of non specific symptoms' were both univariate predictors, the former was chosen. Multivariate logistic regression (Method Enter) identified only one independent predictor for the outcome 'free of symptoms'. Patients with preoperative nonspecific symptoms had a smaller chance to be free of symptoms (*OR* = .21, *p* = .02; 95% *CI*: .14 – .86), or alternatively patients with non-specific symptoms have a greater risk to report biliary and dyspeptic symptoms at one year post-cholecystectomy (*OR* = 2.63, *p* = .043; 95% *CI*: 1.03 – 6.70). No multivariate predictors could be identified for other post operative outcomes.

Predictors of overall QoL and general health at one year were identified by univariate linear regression analyses. QoL was predicted by HTA (β = - .40, *p* < .001), number of non-specific symptoms (β = - .22, *p* = .007), number of dyspeptic symptoms (β = - .35, *p* < .001), preoperative patient group (β = - .23, *p* = .009), only biliary symptoms (β = .26,

p = .003), neurological comorbidity (β = - .22, p = .019), abdominal comorbidity (β = - .23, p = .014), and other comorbidities (β = - .21, p = .026). Predictors were entered simultaneously in a multivariate linear regression with QoL at one year as outcome. Because of high correlations (r = - .91, p < .001) between 'patient group' and 'biliary symptoms only (yes/no)' the latter variable was not entered in multivariate analyses. HTA (β = - .43), patient group (β = - .24), and abdominal comorbidity (β = - .33) predicted overall QoL at one year after cholecystectomy (see Table 5).

Table 4. Univariate predictors of postoperative symptomatic outcomes at one year after cholecystectomy.

Postoperative outcomes	**Predictors**	***OR***	***95% CI***	***p***
Free of symptoms	Only preoperative biliary symptoms	2.48	1.09 – 5.64	.030*
	Cardiovascular comorbidity	.36	.13 – .93	.030*
	Non-specific symptoms (yes/no)	.35	.18 – .67	.002*
	Number of non-specific symptoms†	.62	.43 – .89	.009*
	HTA	.31	.13 – .73	.007*
Only biliary symptoms	–			
Only dyspeptic symptoms	Only dyspeptic symptoms	4.24	1.02 – 17.73	.048*
	Preoperative use of analgesics	.31	.12 – .80	.015*
Biliary and dyspeptic symptoms	–			

* p < .050 indicated statistical significance. Significant results are reported only.
† 'Number of non specific symptoms' was not selected as predictor in multivariate logistic regression

Table 5. Multivariate predictors of overall QoL and general health at one year.

Predictor	***β***	***p***	***Adjusted R^2***	***F***	***p***
HTA	-.43	<.001*			
Patient group	-.24	.033*			
Number of non specific symptoms	.03	n.s.			
Number of dyspeptic symptoms	-.01	n.s.			
Abdominal comorbidity	-.33	.001*			
Neurological comorbodity	-.14	n.s.			
Other comorbidities	-.16	n.s.	.38	7.46	<.001*

* p <.050 indicated statistical significance.

Discussion

Results of cholecystectomy can be disappointing, as clinical decision making is insufficiently tuned to profiles of individual patients. Patient groups based on the clinical picture of gallstone disease showed different patterns of postoperative recovery. Patients with preoperative biliary symptoms only (group 1) were most often free of biliary and dyspeptic symptoms and reported higher overall QoL and general health at one year. At one year, patients with a combination of preoperative biliary and dyspeptic symptoms (group 3) reported most biliary and non-specific symptoms and increased medication use. In the course of one year, overall QoL improved in groups 1 and 3, but not in group 2. Furthermore, preoperative biliary and/or dyspeptic symptoms were not identified as independent predictors of the relief of abdominal symptoms at one year. Patients without non-specific symptoms had a threefold chance to be free of symptoms. In addition, clinical presentation of gallstone disease as well as trait anxiety and abdominal comorbidity had an impact on overall QoL and general health at one year.

Comparison with literature

In the course of one year after cholecystectomy, the report of biliary and dyspeptic symptoms, with exception of lower abdominal pain, decreased. Although 50.0% of the patients are free of symptoms at one year, the prevalence of abdominal symptoms in the sample is higher than the prevalence in the healthy population (21% – 25%)[26, 27]. However, findings of the current study indicate that symptomatic improvements are highly dependent on preoperative symptomatology. Patients in group 1 are most often free of symptoms at one year. Patients in group 2 show minimal improvements of preoperative symptoms (bad taste and flatulence only), whereas patients in group 3 show improvements of practically all biliary and dyspeptic symptoms. In contrast, other studies do not find differential benefits between pre-defined patient groups, such as patients with severe *vs.* mild biliary symptoms[11], or dyspeptic pain symptoms and biliary pain symptoms[17]. The choice of characteristics for stratification may be decisive for the usefulness of group differences. We believe that the most simple model, that is able to differentiate in a meaningful way between patients, should be preferred.

With respect to flatulent dyspepsia which often persists and develops de novo after cholecystectomy[11, 12, 17, 18, 28, 29], a differential symptomatic outcome is found for groups with other preoperative clinical presentations. In group 1 a significant group of patients

developed flatulence after cholecystectomy, whereas a decrease of patients reporting flatulence was observed in group 2 and 3. Furthermore, non-specific symptoms, which were most prevalent in group 3, decreased in groups 1 and 3, but not in the group patients with dyspeptic symptoms only (group 2). Several studies, investigating 12 – 19 months outcome after cholecystectomy, indicated that symptomatic outcome after cholecystectomy could not be predicted[11, 17]. However, our findings suggest that prediction of post-cholecystectomy outcomes is possible and patients with non-specific symptoms have a smaller chance to be free of symptoms at one year. Possibly, a heightened sensitivity for general somatic symptoms or visceral pain, may be the underlying cause of the experience of biliary and dyspeptic symptoms in patients with non-specific symptoms. Additional investigation of the pathology of gastrointestinal symptoms in these patients should clarify, whether biliary or dyspeptic complaints are the most outstanding symptom in the clinical picture.

With respect to the subjective experience of patients, differential improvements in overall QoL were found. Across time a large improvement of overall QoL was found in groups 1 and 3, whereas patients in group 2 did not report an improvement in QoL. As other studies used visual analogue scales to get an impression of the postoperative satisfaction[30] or rated the successfulness of their surgical procedure on self-constructed 4 or 5 point scales[14, 31], comparability of findings is limited. Our findings indicated that patient group and abdominal comorbidity were found to be predictive of overall QoL and general health. This may be in accordance with colicky upper abdominal pain, and steady non-colicky abdominal pain that were found to predict patient satisfaction in another study[30]. Other studies also identified preoperative health status, physical functioning, longer symptom duration, and Chronic Obstructive Pulmonary Disease as predictors of satisfaction[14, 30]. In line with results of QoL in irritable bowel syndrome[32] and breast cancer patients[33], the current study identified HTA has a negative impact on overall QoL at one year.

Recommendations for future research

To investigate pitfalls in clinical decision making in cholecystectomy, comparison of postoperative symptomatic outcomes and QoL measures may be interesting for further study. A review on QoL after laparoscopic surgery recommends the use of a generic and disease-specific HRQoL measure at one and six months[34]. The Short Form 36 Health Survey (SF-36), the Psychological General Well-Being Index (PGWB) and the

Gastrointestinal Quality of Life Index (GIQLI) are recommended as measures. However, these are measures for psychological wellbeing and health status only, whereas a QoL instrument, such as the WHOQOL, not only inquires into patients physical, psychological, and social functioning, but also patients' (dis)satisfaction with that functioning[35, 36 37]. Therefore, future studies should investigate QoL as the subjective evaluation of post-cholecystectomy outcomes. Moreover, the current study demonstrated that non-specific symptoms predict abdominal symptoms at one year. The relationship between non-specific symptoms, such as general malaise, fatigue, weight change and decreased sexual functioning, and the continued experience of gastrointestinal symptoms should be further examined. Furthermore, the impact of HTA on postoperative recovery should be examined in other syndromes than gallstone disease.

Strengths and weaknesses

The present study has several strengths compared with previous studies. It has a prospective design and consecutive patients were included in order to prevent as much as possible a selection bias. Possible differences between participants and dropouts were examined to contribute to maximum generalizability of outcomes. However, some bias may still exist as this is a single centre study. Furthermore, the current study investigated postoperative outcome using self-reported pre- and postoperative symptoms. Although one study showed that only physician-derived information led to valuable predictors[30], we considered the patient's experience as leading. As a recent study demonstrated that physicians underestimate the number and severity of gastrointestinal symptoms in patients[38], we believe that self reports optimally reflect the experience of patients. Furthermore, patients were categorised in three groups based on these self-reported symptoms. A point of criticism may be that nuances may be lost by categorisation. On the other hand, the use of categories enhances the clinical applicability of the results. Finally, the addition of two short evaluative questions indicating overall QoL, that correlate highly with general health in breast cancer survivors[35], gives this study additional value over studies measuring only symptomatic improvement. As QoL and health status represent the patients' well being from a different perspective, it has been recommended to use both measures in clinical decision making[35]. However, it should be acknowledged that the current study can only give an indication of QoL, which is not comparable with a full QoL measurement. We recommend further elaboration of QoL measurements after cholecystectomy.

Implications for clinical practice

The results of this study teach us that close attention should be paid to the clinical picture of gallstone disease, as it gives valuable information for clinical decision making. From the perspective of patient-centered care, patients with different profiles demand a different approach. Although it is often claimed that cholecystectomy is beneficial for both patients with biliary and patients with dyspeptic symptoms, our results show that only patients with purely biliary symptoms should be operated right away. In patients with a combination of biliary and dyspeptic symptoms, cholecystectomy should be considered critically, especially in patients who report many non-specific symptoms. Conservative treatment should be considered in patients with dyspeptic symptoms only, as they show minimal symptomatic benefit and no improvement in QoL after cholecystectomy. Although cholecystectomy is often thought inevitable, risk of postoperative complications such as acute cholecystitis, pancreatitis, or biliary duct obstruction is actually quite small (1%-2% a year)[39, 40]. Besides, after a first biliary attack, only one third of the patients experiences a new attack within a year[41]. Furthermore, physicians should also consider other than abdominal symptoms. The fact that non specific symptoms are identified as the sole predictor of abdominal symptoms at one year, makes clear that the scope of physicians should be broadened from gallstones to the patient as a whole, with his/her abdominal symptoms, non-specific symptoms, and eventually psychological risk factors. Findings of the study also imply that the patient's subjective evaluation of life should be at the core of a patient-centred approach. Information of patients should be tailored to the individual patient's profile and based on improvements of QoL. The preoperative clinical picture has an effect on QoL, as patients with biliary symptoms only experience best QoL postoperatively. Furthermore, HTA and abdominal comorbidity have a negative impact on QoL. Instead of symptomatic outcome, QoL should be taken as a starting point for clinical decision making in cholecystectomy. As cholecystectomy is an elective procedure, the performance should be considered in terms of gain of QoL, based on the patient's clinical picture. Optimally, clinical decision making in elective cholecystectomy should be a collective choice of the doctor and patient, instead of a case of doctors only. Changing common practice in gallstone disease will eventually lead to a decrease of unsuccessful cholecystectomies in patients with atypical biliary symptoms, and eventually to greater cost-effectiveness.

In conclusion, preoperative symptoms are relevant for clinical decision making, as patients with only biliary symptoms show the best symptomatic and QoL outcomes at

one year. Cholecystectomy is not beneficial for patients with only dyspeptic symptoms, as they experience minimal symptomatic improvements and no improvement in QoL across time. Overall, patients with non-specific symptoms have a greater risk of negative symptomatic outcome, whereas patients with HTA and abdominal comorbidity have a greater risk of low QoL at one year after cholecystectomy.

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Chapter 7

Predictors of quality of life after gallbladder surgery: A one year prospective follow-up study

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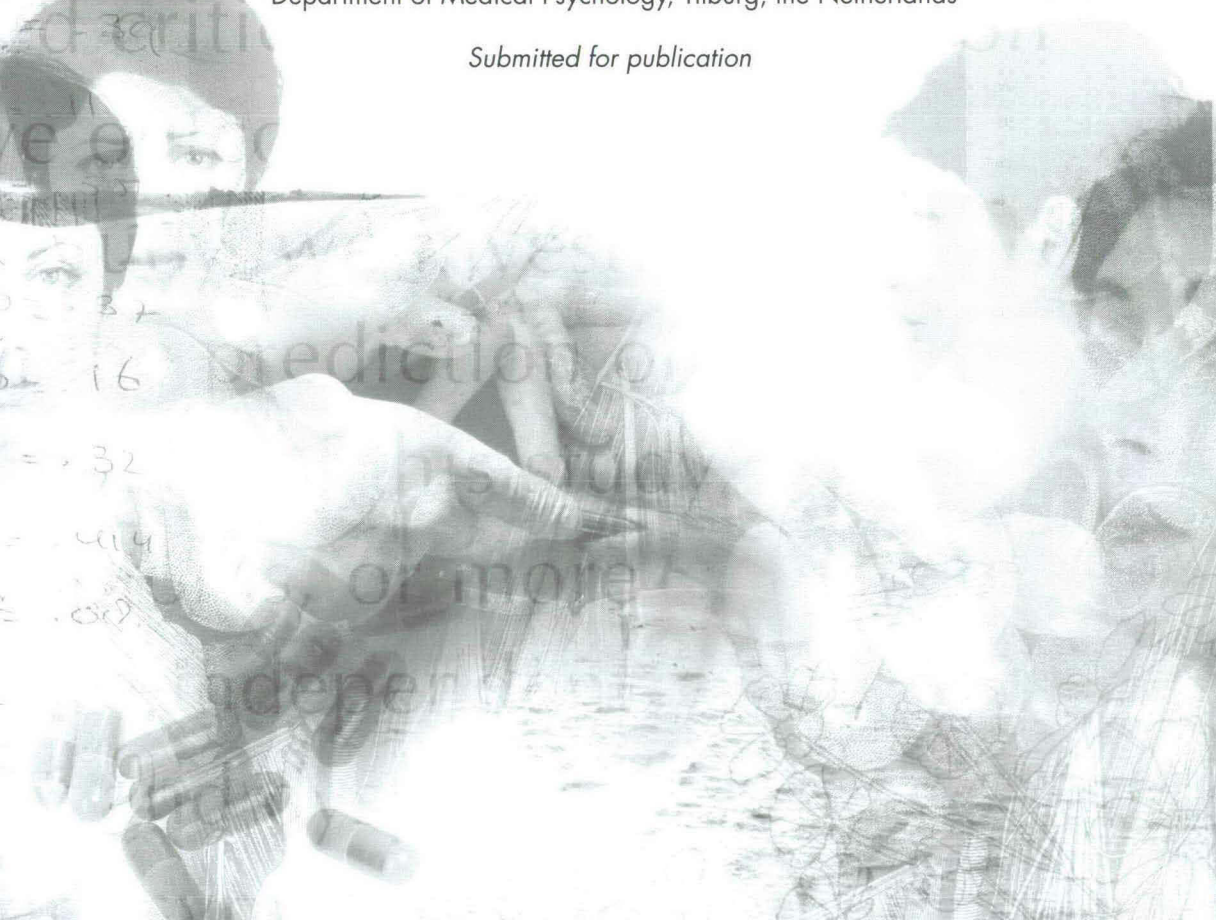


Abstract

Purpose: Removal of the gallbladder (cholecystectomy) is considered as the golden standard in gallstone disease. The aims of the current study are to investigate changes in quality of life (QoL) and to identify predictors of QoL one year after cholecystectomy.

Methods: Consecutive patients (n = 142), age 18 – 65 yrs, with uncomplicated symptomatic gallstone disease, awaiting an elective cholecystectomy, completed a symptom checklist and psychological questionnaires (WHOQOL-BREF, STAI, CES-D, FAS), pre-operatively, six weeks, and one year after surgery.

Results: One year after cholecystectomy, QoL had improved (ε^2 = .04 – .35) in all domains except Social Relationships. This improvement was reached within the first six weeks after surgery. Preoperative fatigue (β : - .23 to - .45) and trait anxiety (β : - .30 to - .48) were the strongest predictors of QoL at one year. Fatigue (β : - .21 to - .30) and trait anxiety (β = - .30) had a negative impact on improvements in QoL, whereas depressive symptoms had a positive impact on QoL (β = .59).

Conclusion: Cholecystectomy results in improvements in QoL. Negative effects of psychological risk factors on QoL may be minimised by psychological interventions.

Introduction

Gallstone disease is a common condition which affects 5% to 22% of all people in Western countries[1-3]. However, gallstone disease often remains clinically undiagnosed as only 10% – 30% of all patients experience symptoms[4-7], such as upper abdominal pain or dyspeptic symptoms. Elective cholecystectomy, or surgical removal of the gallbladder, is the treatment of choice in uncomplicated symptomatic gallstone disease. However, 13% – 44% of the patients report negative outcomes after cholecystectomy, such as persisting symptoms and pain[8-13]. Studies who attended the patient's subjective experience after cholecystectomy found high rates for patient satisfaction (96.8% – 97.6%)[14, 15] and improvements of Health Related Quality of Life (HRQoL)[16-19]. However, all studies measured HRQoL, which is the impact of gallstone symptoms on life, and did not measure Quality of Life (QoL), which is a subjective evaluation of the individual's health status, psycho-social status, and other aspects of life (World Health Organization). With regard to the issue of patient centered care, QoL measures should be preferred above HRQoL.

Insight in risk factors of negative outcomes or dissatisfaction after cholecystectomy is important to establish a patient tailored approach and inform patients adequately about individual-specific risks. Both clinical[14, 20-22] and psychological factors[20, 23-25] are found to predict objective health outcomes after cholecystectomy. However, predictors of subjective outcomes are less understood. One study found that asymptomatic patients with high surgical risks were at risk of worse improvement of HRQoL three months after cholecystectomy[26]. Another study found that good, fair or poor preoperative health status, worse physical functioning, symptom duration > 6 months, and previous episode of cholecystitis predicted an unsuccessful outcome after cholecystectomy[14]. However, the impact of psychological factors on QoL outcomes after cholecystectomy has not been examined so far. Therefore, the objectives of this study were to investigate changes in QoL within one year after cholecystectomy and to identify clinical and psychological predictors of QoL.

Methods

Patients

Patients were recruited from the Department of Surgery of the St. Elisabeth Hospital in Tilburg, the Netherlands. Consecutive patients (18 – 65 years) with diagnosed symptomatic cholelithiasis, awaiting an elective laparoscopic cholecystectomy who visited the hospital

between March 2006 and January 2008, were eligible for the study. Exclusion criteria were: patients with ASA III or IV, undergoing an emergency procedure or intended open cholecystectomy, insufficient knowledge of the Dutch language, choledocholithiasis, cholangitis, known pregnancy, known liver-cirrhosis, history of abdominal malignancy, previous upper abdominal surgery (precluding laparoscopic approach), and psychiatric diseases. All patients underwent a standard surgical and anaesthetic procedure. The protocol of the study was approved by the local ethics committee.

Procedure

Preoperatively, participation was asked during the patients' first surgical consultation at the outpatient clinic. The surgeon introduced the study, whereas subsequently nurses informed patients about the research procedures. Patients received the first set of questionnaires, which also contained written information about the study, and signed informed consent. Medical history and comorbidities were obtained from medical records. Patients completed and returned the first questionnaires before admission for cholecystectomy. If necessary, patients received a reminder telephone call to return the questionnaires three to five days before the operation. Patients who returned the questionnaires after admission were excluded from the study. At six weeks and one year after cholecystectomy, patients received the same questionnaire which could be returned in a prepaid envelope. If needed, patients were contacted by telephone twice, usually two and four weeks after sending the questionnaires. Patients who returned their second or third questionnaire later than 3 months or 15 months, respectively, were considered as non-responders.

Questionnaires

The demographic questionnaire was completed preoperatively and asked about sex, age, marital status, educational level, and work. Other self report information, with exception of the STAI trait scale, was obtained three times, namely preoperatively, at six weeks, and one year after cholecystectomy.

Patients completed a symptom checklist that was based on information from focus groups. Patients ticked off whether they experienced biliary symptoms (upper abdominal pain, nausea, vomiting)[14], dyspeptic symptoms (bad taste, heartburn, under abdominal pain, diarrhoea, flatulence)[14], and non-specific symptoms (general malaise, weight-change, decrease in sexual functioning, health complaints not mentioned in the pre-defined

checklist) in the past week. All patients included had experienced biliary or dyspeptic symptoms in medical history.

Patients also completed the WHOQOL-BREF, which is a short version of the generic multi-dimensional WHOQOL-100, originally developed by the World Health Organization[27]. The WHOQOL-BREF consists of 26 items with a 5 point Likert-scale measuring QoL on in four different domains (Physical, Psychological, Social, and Environment). Two benchmark items display overall QoL and health. The WHOQOL-BREF has been cross-culturally validated and has good psychometric properties, such as good internal consistency (Cronbach's $\alpha > .70$) and adequate test retest reliability, constructive and discriminative validity[28-31].

The Center of Epidemiological Studies Depression Scale (CES-D)[32] was completed preoperatively, at six weeks and one year follow-up. The CES-D has a 4-point Likert scale indicating how often patients had experienced depressive symptoms in the week before. The 16-item version used in this study measures two independent factors, namely Depressed Affect and Positive Affect, and is a valid measure for depressive symptoms in the general population[32]. The CES-D has good internal consistency (Cronbach's $\alpha = .75 - .88$).

Patients also completed the Fatigue Assessment Scale (FAS)[33], which consists of 10 items with a 5-point rating scale indicating how often patients feel tired usually. The FAS has has an excellent internal consistency (Cronbach's $\alpha = .90$)[34] and good reliability[33].

The Dutch versions of the Spielberger State-Trait Anxiety Inventory (STAI), consists of two scales of 20 items each with a 4-item Likert-scale reflecting the extent of anxiety patients feel at a specific moment in time (state anxiety) and patients generally feel (trait anxiety)[35]. Preoperatively, patients completed both scales, whereas at follow-up at six weeks and one year, only the STAI State scale was completed. The STAI has good and moderate test-retest reliability for State anxiety ($r = .84 - .88$) and trait anxiety ($r = .30 - .73$)[36]. Internal consistency is high for both the state- and trait anxiety scale (Cronbach's $\alpha = .93 - .96$) and (Cronbach's $\alpha = .92 - .93$), respectively)[35, 36].

Statistical procedures

Differences between outcomes at two time points were investigated by Paired *t*-tests and Wilcoxon Signed Ranks test. Measures of overall change (3 time points) were obtained by one way repeated-measures ANOVA. Results were checked for sphericity and, dependent from outcome, ANOVA's were interpreted as univariate tests (using Greenhouse Geiser or Huynh-Feldt correction when appropriate) or as multivariate tests (using Wilk's Lambda). Friedman's test was used to investigate changes in symptom report in the course of one

year. In case of a significant change, paired *t*-Tests were performed to investigate the change in QoL between two time points. Difference scores between the preoperative QoL and QoL at one year were calculated for each domain of the WHOQOL-BREF and overall QoL and health.

Multivariate linear regression analyses (Method Forward Stepwise) were performed to investigate preoperative psychosocial variables and symptoms as predictors of QoL at one year. Prior to multivariate regression, correlations between preoperative clinical and psychosocial variables and QoL at one year (Pearson's product moment correlation and Spearman's Rank order correlation) were calculated to check for multicollinearity and singularity. None of the correlations between FAS, CES-D, STAI state, STAI trait anxiety, preoperative symptoms and QoL exceeded > .70. Stepwise regression was performed. Stepwise regression implicates that predictors are entered in the regression equation one by one, starting with the strongest predictor. Redundant predictors ($p > .050$) are removed from the regression analysis each time a new predictor is added. To minimise the number of predictors in the regression analyses, several sets of predictors were investigated separately. Preoperative symptom group (nominal item) and non-specific symptoms (dichotomised item) were inserted as predictors besides fatigue, depressive feelings, and state and trait anxiety (set I). Further investigation of biliary, dyspeptic, and non-specific symptoms (set II), and psychosocial variables (set III) resulted in a selection of significant predictors for in the final regression analyses (set IV).

Multivariate linear regression was performed with difference scores in QoL as outcome. First of all, preoperative symptom group, non-specific symptoms, fatigue, depressive symptoms, and state and trait anxiety were inserted as variables (set V). After investigating biliary, dyspeptic, and non-specific symptoms (set VI), and psychosocial variables (set VII) separately, significant predictors were entered in final regression analyses (set VIII). A p value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 17.0.

Results

In total 266 patients were approached for participation, of which 250 patients participated in the study. At one year, 144 patients had returned their questionnaires at all three time points (preoperatively, six weeks and one year) (overall response rate: 57.6%). A flow chart of the study participation is shown in figure 1.

Patients that did not respond or ended participation within one year did not differ on demographic variables, preoperative symptom report, comorbidities, medication use, and psychosocial variables from participants. Demographic characteristics of the sample are shown in table 1. Preoperative symptom report, comorbidities, medication use, and values of psychosocial and QoL measures are reported in table 2.

Figure 1. Flowchart of the population under study.

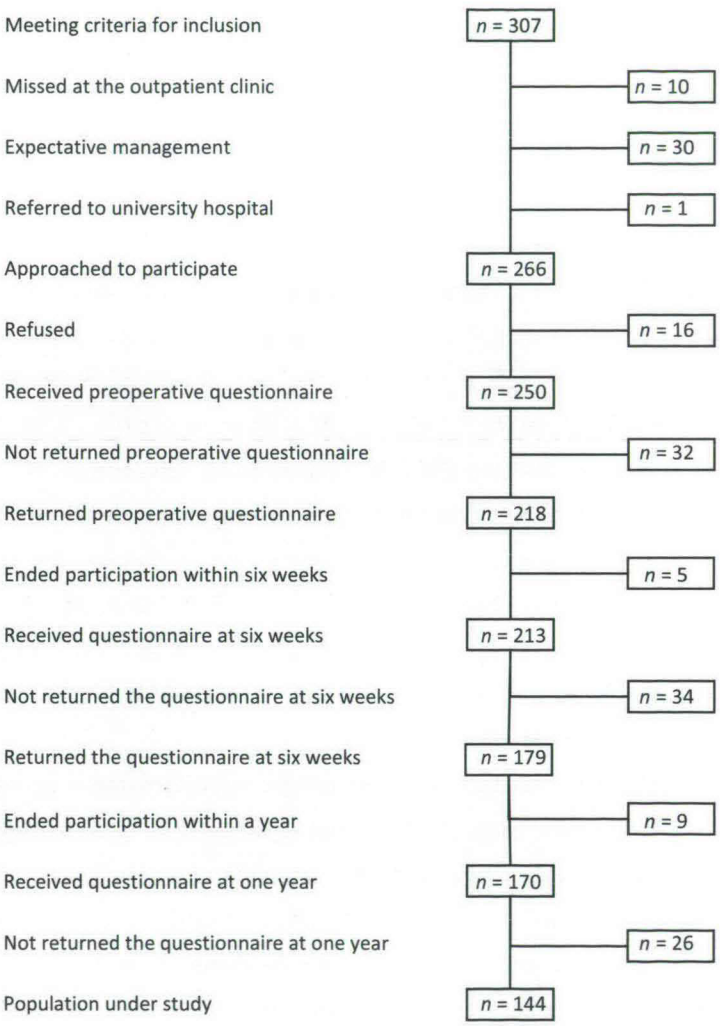


Table 1. Demographic characteristics (n = 142).

Demographic characteristics	
Female patients (%)	76.8
Age (M ± SD)	47.04 ± 12.14
Highest level of education	
Primary or lower vocational education (%)	17.7
Secondary education (%)	48.2
Higher education (%)	7.1
Higher professional education or university (%)	27.0
Working under payment (%)	70.2
Marital status	
Single (%)	4.3
Widowed or divorced (%)	5.7
Married or cohabitant (%)	90.0

Postoperative measures

Between baseline and one year follow-up, QoL significantly improved in all domains, except the QOL domain Social Relationships (Figures 2a and 2b). In the first six weeks after cholecystectomy, QoL improved significant in the domains Physical Health (t = - 8.64, p < .001), Psychological Health (t = - 3.27, p = .001), Environment (t = - 3.34, p = .001), and overall QoL (t = - 6.15, p < .001), but not in the domain Social Relationships (t = - .67, p = .50). In the period between 6 weeks and one year after surgery no significant changes were observed. The same pattern was observed for state anxiety and depressive symptoms (see figures 3a and 3b). Both state anxiety and depressive feelings decreased significantly in the first six weeks after surgery ((t = 4.53, p < .001) and (t = 3.46, p = .001), respectively). No changes were observed in the period between six weeks and one year. With regard to fatigue, no differences were found.

In the course of one year, all individual biliary and dyspeptic symptoms decreased with the exception of diarrhoea (see Table 2). The number of patients experiencing non-specific symptoms remained stable over time. With the exception of diarrhoea (Z = - .58, p = .564), the report of individual biliary and dyspeptic symptoms changed within the first six weeks, but not in the period between six weeks and one year after cholecystectomy. The use of analgesics (F = .63, p = .54), psychotropic medication (F = .93, p = .40), and other medication (F = .93, p = .40) remained stable over time.

Table 2. Pre- and postoperative clinical and psychosocial characteristics.

Clinical characteristics	Preoperatively	6 weeks	One year	$p^{\ddagger}$
Free of symptoms (%)	0.0	44.4†	50.3	<.001*
Biliary symptoms (%)	24.2	3.5†	8.4†	.024*
Upper abdominal pain (%)	69.5	19.0†	22.4	<.001*
Nausea (%)	40.1	14.1†	9.1	<.001*
Vomiting (%)	19.0	1.4†	2.8	<.001*
Dyspeptic symptoms (%)	14.5	30.3†	23.3†	.010*
Bad taste (%)	21.1	9.9†	7.7	<.001*
Heartburn (%)	69.5	16.9†	16.8	.03*
Lower abdominal pain (%)	19.7	8.5†	11.9	.008*
Diarrhoea (%)	17.6	14.8	9.8	.11
Flatulence (%)	36.6	26.1†	21.8	.008*
Biliary and dyspeptic symptoms$^{\downarrow}$ (%)	61.3	21.8†	17.5	.001*
Non-specific symptoms (%)	27.5	26.1	21.0	.52
General malaise (%)	9.9	3.5	5.6	.07
Weight change (%)	2.8	11.3†	8.4	.02*
Decreased sexual functioning (%)	9.9	4.9	7.0	.13
Other non-specific health complaints(%)	14.1	9.9†	6.3	.02*
Co-morbidities				
Coronary arterial disease (%)	18.9			
Pneumonal disease (%)	5.7			
Abdominal disease (%)	27.4			
Kidney disease (%)	.9			
Urogenital disease (%)	8.5			
Neurological disease (%)	8.5			
Other comorbidities (%)	49.1			
Self-reported medication use				
Analgesics (%)	35.9	35.8	29.2	.53
Psychotropic medication (%)	10.6	19.4	19.0	.31
Other medication (%)	50.7	80.6	85.7	.40
Psychosocial characteristics				
Trait anxiety (STAI Trait) (M ± SD)	36.89 ± 9.69			
State anxiety (STAI State) (M ± SD)	38.7 ± 11.50	34.62 ± 10.53†	35.71 ± 10.41	<.001*
Fatigue (FAS) (M ± SD)	22.37 ± 5.22	21.92 ± 5.08	22.82 ± 5.99	.22
Depressive symptoms (CES D) (M±SD)	22.63 ± 7.14	20.79 ± 6.49†	21.38 ± 7.34	.006*
QoL domains (WHOQOL-BREF)				
Physical Health (M ± SD)	14.14 ± 2.74	15.99 ± 2.75†	15.75 ± 2.92	<.001*
Psychological Health (M ± SD)	14.68 ± 2.64	15.26 ± 2.76†	15.19 ± 2.69	.003*
Social Relationships (M ± SD)	15.87 ± 2.67	16.00 ± 2.83	15.76 ± 2.91	.42
Environment (M ± SD)	15.72 ± 2.19	16.23 ± 2.48†	16.06 ± 2.36	.008*
Overall QoL and general health (M ± SD)	7.19 ± 1.72	7.93 ± 1.55†	7.77 ± 1.65	<.001*

* $p < .050$ indicated statistical significance.

† Significant change ($p < .050$) compared to the measurement at former time point.

‡ *p*- values obtained from differences between preoperative measures and measures at one year.

$^{\downarrow}$ Combination of ≥ 1 biliary symptoms (upper abdominal pain, nausea, and vomiting) *and* ≥ 1 dyspeptic symptoms (bad taste, heartburn, lower abdominal pain, diarrhoea, and flatulence).

Figure 2a. Post-cholecystectomy changes in QoL within the domains Physical Health, Psychological Health, Social Relationships, and Environment.

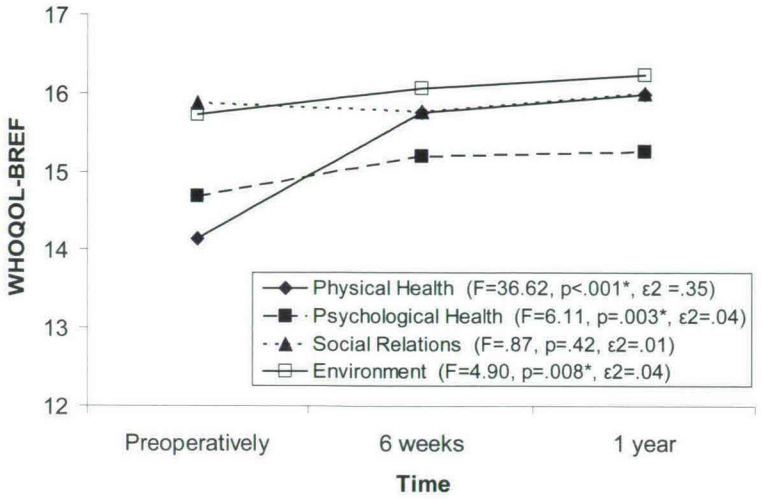


Figure 2b. Post-cholecystectomy changes in overall QoL and general health in the course of one year after cholecystectomy.

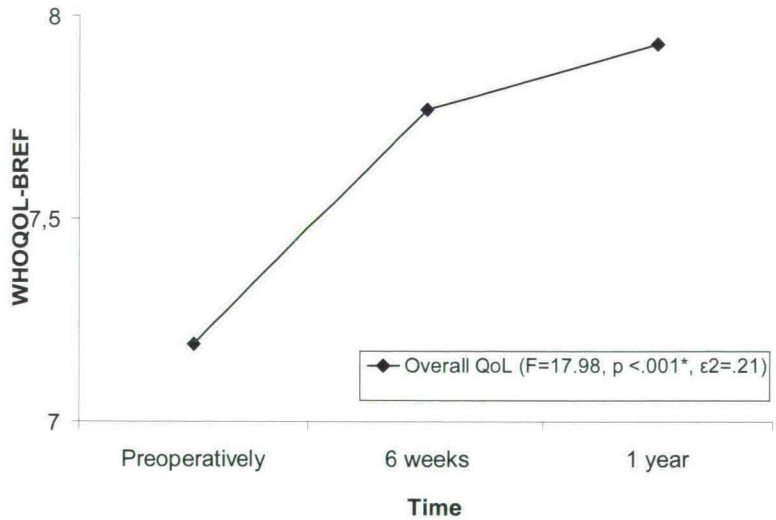


Figure 3a. Changes in state anxiety in the course of one year after cholecystectomy.

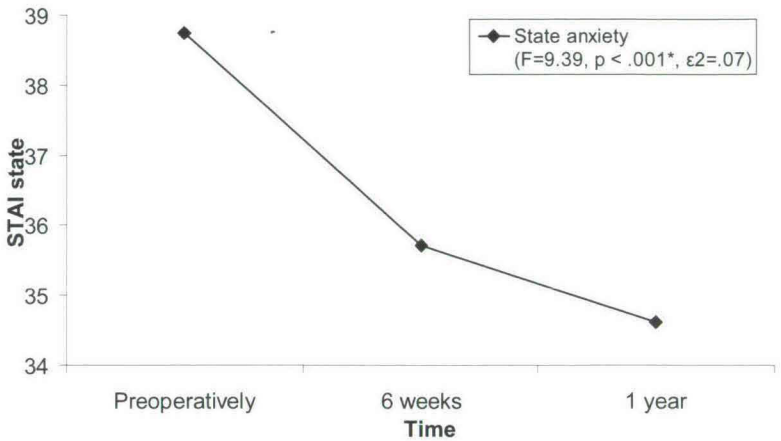
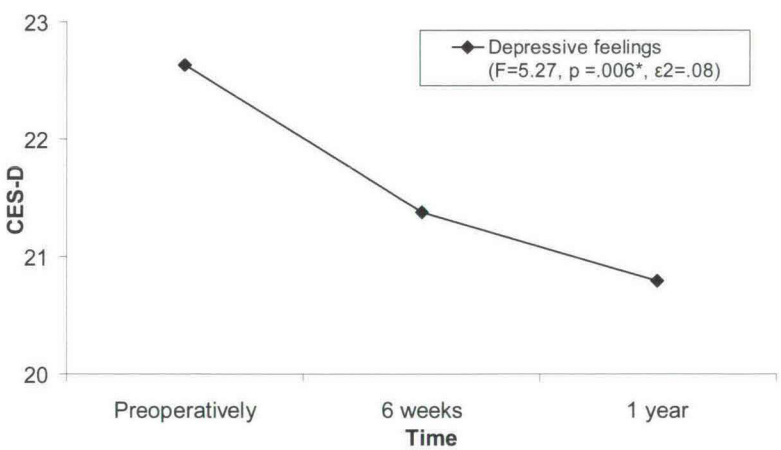


Figure 3b. Changes in depressive feelings in the course of one year after cholecystectomy.



Prediction of QoL at one year after surgery

Results of multivariate regression analyses (set I) are shown in table 3. Preoperative symptoms (only biliary symptoms, only dyspeptic symptoms, or a combination of both) did not predict any of the domains of QoL at one year.

In the subsequent analyses separate preoperative symptoms were entered as predictors in a multivariate regression with each domain of QoL as outcome (set II). Physical health was

predicted by diarrhoea (β = - .27, p = .001), bad taste (β = - .20, p = .015), and other non-specific symptoms (β = - .18, p = .024; adjusted R^2=.131, F = 7.93, p < .001). Psychological health was predicted by general malaise (β = - .18, p = .007), other non-specific symptoms (β = - .25, p = .001), lower abdominal pain (β = - .21, p = .008), and heartburn (β = - .16, p = .040; adjusted R^2 = .203, F = 9.77, p < .001). QoL in the domain Social Relationships was predicted by several preoperative symptoms, namely general malaise (β = - .18 , p = .037), other non-specific symptoms (β = - .27 , p = .001), decreased sexual functioning (β = - .22, p = .009), heartburn (β = - .20, p = .010), and weight change (β = .16, p = .034; adjusted R^2 = .250, F = 10.14, p < .001). With respect to Environment, QoL was predicted by other non-specific symptoms (β = - .30, p = <.001) and diarrhoea (β = - .18, p = .025; adjusted R^2 = .106, F = 9.15, p < .001). Overall QoL was predicted by general malaise (β = - .14, p = .088), lower abdominal pain (β = - .16, p = .058), bad taste (β = - .17, p = .040), and diarrhoea (β = - .17, p = .043; adjusted R^2 = .121, F = 9.15, p < .001). Investigation of psychological variables (set III) indicated that fatigue and state anxiety predicted Physical Health at one year after cholecystectomy ((β = = - .37, p < .001) and (β = - .26, p = .002), respectively; adjusted R^2 = .292, F = 25.50, p <. 001). Depressive symptoms (β = - .37, p < .001) and trait anxiety (β = - .38, p < .001) were independent predictors of Psychological Health at one year (adjusted R^2 = .441, F = 47.92, p < .001). QoL in the domain Social Relationships was predicted by depressive symptoms (β = - .31, p = .002) and trait anxiety (β = - .25, p = .014; adjusted R^2 = .233, F = 19.06, p < .001), whereas QoL in the domain Environment was predicted by trait anxiety only (β = - .46, p < .001; adjusted R^2 = .207, F = 32.11, p < .001). Overall QoL and health was independently predicted by trait anxiety and fatigue ((β = - .38, p < .001) and (β = - .23, p = .014), respectively; adjusted R^2 = .282, F = 24.26, p < .001). Subsequently, all psychological and clinical variables that emerged from the separate analyses (sets II and III) were entered simultaneously in a multivariate regression analysis (Method stepwise forward) with the different domains of QoL as outcome (set IV). Results of these analyses are presented in table 4.

Table 3. Independent predictors of QoL at one year after cholecystectomy.

QoL at one year (WHOQOL-BREF domains)	Independent Predictor	*β*	Adjusted R^2 change	Adjusted R^2	*F*	*p*
Physical Health	Fatigue	-.45	.310			
	State anxiety	-.21	.033	.329	24.30	< .001*
Psychological Health	Trait anxiety	-.30	.356			
	Depressive symptoms	-.29	.095			
	Fatigue	-.23	.031	.464	28.45	< .001*
Social Relationships	Fatigue	-.42	.271			
	Non-specific symptoms	-.30	.077	.333	24.51	< .001*
Environment	Trait anxiety	-.48	.233	.224	28.19	< .001*
Overall QoL	Trait anxiety	-.33	.229	.254	17.14	< .001*

Multimariate linear regression was performed (Method Stepwise) inserting preoperative depressive symptoms, fatigue, anxiety state, trait anxiety, preoperative symptom category and non-specific symptoms.

* $p < .050$ indicated statistical significance.

Table 4. Preoperative symptoms and psychological variables as independent predictors of QoL at one year after cholecystectomy .

QoL at one year (WHOQOL-BREF domains)	Independent Predictor	*β*	Adjusted R^2 change	Adjusted R^2	*F*	*p*
Physical Health[a]	Fatigue	-.36	.244			
	State anxiety	-.26	.060			
	Diarrhoea	-.18	.030	.318	21.65	< .001*
Psychological Health[b]	Trait anxiety	-.38	.358			
	Depressive symptoms	-.37	.092	.450	47.92	< .001*
Social Relationships[c]	Depressive symptoms	-.31	.206			
	Trait anxiety	-.25	.040	.495	19.06	< .001*
Environment[d]	Trait anxiety	-.41	.214			
	Non-specific symptoms	-.17	.027	.230	20.52	< .001*
Overall QoL[e]	Trait anxiety	-.38	.255			
	Fatigue	-.23	.038	.282	26.96	< .001*

Procedures of multivariate linear regression (Method stepwise forward) (set IV) are described in the Method section.

* $p < .05$ indicated statistical significance.

[a] Variables bad taste and other non specific symptoms were not selected in the final regression model; [b] Variables general malaise, other non specific symptoms, lower abdominal pain, and heartburn were not selected in the final regression model; [c] Variables general malaise, other non specific symptoms, decreased sexual functioning, heartburn, and decreased sexual functioning were not selected in the final regression model; [d] The variable diarrhoea was not selected in the final regression model; [e] Variables general malaise, lower abdominal pain, bad taste, and diarrhoea were not selected in the final regression model.

In order to control for QoL scores at baseline, the same regression analyses were performed with difference scores in QoL as outcome and preoperative psychological variables, preoperative symptom groups, and non specific symptoms as possible predictors (set V). Results of these analyses are shown in table 5. No predictors were found for differences in QoL within the domains Psychological Health, Environment, and overall QoL and health. When separate preoperative symptoms were entered as predictors in multivariate regression analyses with difference scores in QoL as outcome (set VI), the following results were found. Preoperative vomiting and flatulence predicted differences in Physical Health ((β = .18, p = .03) and (β = .17, p = .046), respectively; adjusted R^2 = .052, F = 4.73, p = .010). Changes in QoL within Social Relationships were predicted by general malaise (β = - .17, p = .048; adjusted R^2 = .021, F = 3.93, p = .048). Other non-specific symptoms was the only predictor of changes in QoL within the domain Environment (β = - .21, p = .014; adjusted R^2 = .044, F = 6.24, p = .014). No predictors were identified for improvements in the domains Psychological Health, Social Relationships and overall QoL and health.

Likewise, all psychological variables were entered to investigate which variables predicted difference scores in QoL (set VII). Depressive symptoms (β = .61, p < .001), fatigue (β = - .31, p = .006), and trait anxiety (β = - .25, p = .03) predicted changes in Physical Health in the course of one year (adjusted R^2 = .212, F = 10.86, p < .001). Fatigue was the only predictor of changes in the domain Social Relationships (β = - .22, p = .02; adjusted R^2 = .041, F = 5.66, p = .019). None of the psychological variables predicted changes in QoL within the domains Psychological Health and Environment. Depressive symptoms and trait anxiety predicted changes in overall QoL and health in the first year after cholecystectomy ((β = .37, p = .001) and (β = - .27, p = .049), respectively; adjusted R^2 = .078, F = 5.64, p = .005).

Finally, predictors from sets VI and set VII were entered simultaneously in multivariate linear regression with changes in QoL within each domain as outcome (set VIII). Results of these analyses are shown in table 6. No predictors were found for the outcome differences in QoL with respect to the domain Psychological health.

Table 5. Independent predictors of difference scores of QoL at one year after cholecystectomy.

QoL at one year (WHOQOL-BREF domains)	Independent Predictor	β	Adjusted R^2 change	Adjusted R^2	F	p
Physical Health	Depressive symptoms	.59	.066			
	Trait anxiety	-.30	.130			
	Fatigue	-.30	.051	.222	10.06	< .001*
Social Relationships	Fatigue	-.21	.046	.036	4.48	.037*

Multivariate linear regression (Method stepwise forward) was performed inserting preoperative depressive symptoms, fatigue, state anxiety, trait anxiety, preoperative symptom category, and non-specific symptoms.

* $P < .05$ indicated significance. Significant results are reported only.

Table 6. Independent predictors of difference scores of QoL at one year after cholecystectomy.

QoL at one year (WHOQOL-BREF domains)	Independent Predictor	β	Adjusted R^2 change	Adjusted R^2	F	p
Physical Health[1]	Depressive symptoms	.58	.083			
	Fatigue	-.28	.093			
	Flatulence	.25	.042			
	Trait anxiety	-.31	.052	.243	10.32	< .001*
Social Relationships[2]	General malaise	-.17	.028	.021	3.93	.048*
Environment	Other non-specif. sympt.	-.21	.045	.038	6.34	.013*
Overal QoL and Health	Depressive symptoms	.35	.041			
	Trait anxiety	-.25	.043	.068	5.27	.006*

Procedures of multivariate linear regression (Method stepwise forward) (set VII) are described in the Method section.

* $p < .05$ indicated statistical significance. Significant results are reported only.

[1] Preoperative vomiting was not selected as predictor in the final regression model;

[2] Fatigue was not selected as predictor in the final regression model.

Discussion

Despite the high percentages of patients reporting persisting symptoms, cholecystectomy remains the golden standard in gallstone disease. As cholecystectomy is an elective procedure intended to improve and *not* to save the patient's life, it is important to evaluate post-cholecystectomy outcomes from the perspective of the patient. One year after elective cholecystectomy, the current study showed improvements in all domains of QoL, except in the domain of Social Relationships. Furthermore, the report of biliary and dyspeptic symptoms, depressive symptoms and state anxiety decreased in the course of one year. Improvements in symptom report and QoL took place within the first six weeks after surgery. Preoperative fatigue and trait anxiety had a negative impact on QoL at one year after cholecystectomy. The impact of preoperative biliary and dyspeptic symptoms was limited: only diarrhoea had a small negative effect on the QoL domain Physical Health. Preoperative fatigue and trait anxiety also had a negative effect on relative improvements in QoL in the course of one year. Furthermore, patients with depressive symptoms had greater relative improvements in QoL. Flatulence was the only disease-specific symptom with some clinical relevance for improvements in QoL.

The current study showed overall symptomatic benefit in the first year after cholecystectomy. Consistent with other studies[11, 12, 17, 22, 37], diarrhoea was the only symptom that did not improve. In fact, diarrhoea often persists or emerges after cholecystectomy and is associated with the post-cholecystectomy syndrome[16]. Symptoms, QoL, and psychological variables improved all within the first six weeks after surgery. This is the time frame in which patients normally return to work after cholecystectomy[38]. A study investigating health status at 2 and 12 months, also found that the improvements after cholecystectomy occurred within the first two months after surgery[39]. In contrast, another study using multiple measurements (6, 12, and 60 months)[40], found no long term improvements in psychological well being and health status. This difference may be due to the longer period of follow-up and small sample size. Besides another report from the same sample[21], no other studies have investigated objective or subjective outcomes at six weeks postoperatively. The current study suggests that postoperative recovery < 6 weeks is the most informative, which should be further investigated by future studies.

So far, the current study appears to be the first study investigating QoL after cholecystectomy. The WHOQOL group defined QoL as a multidimensional concept integrating 'an individual's perception of his/hers position in life in the context of the culture

and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns' [27]. Other outcome studies assessed health status[15, 16, 26, 41, 42 17, 19, 43], which is the objective degree of disability[44]. In addition, several studies used subjective ratings indicating satisfaction with the result of cholecystectomy[14, 15, 45]. Since QoL and health status are related, but different concepts[46, 47], a comparison with other studies is hampered. Moreover, comparability of studies is also hampered by differences in time points of investigation (3 months to 5 years postoperatively). At three months after cholecystectomy, general improvements in health status were only found in patients with low surgical risks[43]. At 4 and 17 months after cholecystectomy[16, 17], greatest improvements in health status were found in the dimensions gastrointestinal symptoms, physical health and bodily pain. With regard to psychological well-being long term improvements were observed[17, 41], although psychological functioning did not seem to improve[16]. In line with these findings, the current study demonstrated large improvements in the domain Physical health and in the general evaluative facet overall QoL and health, but also small improvements within the domains Psychological health and Environment. Although other studies demonstrated a small, but significant, improvement on the dimension of social functioning[16, 17 43], the current study did not find improvement in the QoL domain Social Relationships. This discrepancy was also found in breast cancer patients[47].

The present study implicated that preoperative fatigue has a negative effect on QoL in the domain Physical health. Trait anxiety had a negative impact on Psychological health, Environment, and overall QoL and health. Trait anxiety is also found to be a predictor of QoL in the irritable bowel syndrome[48] and breast cancer[49]. Clinical biliary and dyspeptic symptoms and pain have been identified as predictors of objective outcomes[14, 20-22] and were found to be associates of postoperative satisfaction[45]. However, preoperative clinical biliary and dyspeptic symptoms had no impact on QoL at one year. Besides, the impact of theses symptoms on health status in patients with symptomatic gallstone disease has not been investigated so far. With the exception of one study[43], absolute QoL scores were subject of this research whereas improvement in QoL should be the focus, as this gives an impression of benefit from the perspective of the patient.

Predicting post-cholecystectomy improvements in QoL, psychosocial factors outweigh clinical factors. Notably, patients with high preoperative depressive symptoms experienced greater improvements in QoL within the domains Physical health and overall QoL and health. This effect may be indirect as non-pathological depressive symptoms are moderately correlated to QoL[30, 50, 51 48]. As a reaction to physical illness and the prospect of undergoing

surgery, patients may experience more depressive symptoms, preoperatively. Moreover, non-specific clinical factors offer a small negative contribution to improvements in QoL, whereas flatulence offers a positive contribution to QoL improvements.

The study has several limitations that need to be acknowledged. First of all, because of the use of multiple measurements and a long term follow-up, the response rate is moderate. However, the integration of three measurements in the design gives us valuable insights in the process of post-cholecystectomy recovery that otherwise would be overlooked (e.g. the fact that all improvements take place within 6 weeks). Secondly, as clinical experience shows that patients experience greatest improvements within six weeks[38] we selected six weeks as appropriate moment for the first follow-up. Possibly, significant improvements take place earlier. As evidence exist that patients generally return to work after one or two weeks[37, 52] and take up activities at two to six days after cholecystectomy[42, 52], an earlier time point would be more appropriate. Future studies may address this issue, determining the critical period of post-cholecystectomy recovery with objective and subjective measures. Furthermore, in the current study there was not controlled for the impact of co-morbidities, age, and sex on QoL, as we aimed at a parsimonious model. However, as women are found to have higher trait anxiety[53], sex should at least be a factor controlled for in future studies. Besides, special life events and changes in comorbid conditions in the course of one year should also be an issue to control for. Moreover, we used a self-constructed checklist for pre- and postoperative symptoms, based on clinical experience, information of focus groups, and other existing checklists[14]. To improve comparability with other studies, the use of a standardised disease-specific symptom checklist should be preferred. However, to our knowledge such a checklist is not yet developed for cholelithiasis.

The results of this study may have implications for clinical practice. Symptoms and postoperative pain are traditionally used as benchmarks for surgical procedures. However, from the perspective of a patient tailored approach, the patient's QoL should be leading in the choice between treatment options. Information of patients should concentrate on improvements in QoL, and patients should be involved weighing the pros and cons of cholecystectomy in consultation with their surgeon. Secondly, as psychosocial factors surpass the effect of clinical risk factors, these risk factors need to be more attended to during surgical consultation. Preoperative screening for fatigue and trait anxiety would have added value for the consideration of cholecystectomy and the information of patients. Ultimately, it should be considered whether cholecystectomy is the preferred treatment for gallstone disease in patients with high fatigue and high trait anxiety. If minimal

improvements are to be expected wait and see could be an alternative, especially since the risk of complications of such a wait and see policy is small (1% – 2% a year)[54, 55], whereas the risk of peri- and postoperative complications is also small but not neglectable (0.6% – 5.0%)[56, 6]. Preoperatively, psychological interventions may be started to teach patients with high trait anxiety how to cope with fatigue and heightened anxiety. Minimising the negative effect of their psychological constellation, patients may report greater benefit in QoL after cholecystectomy.

In conclusion, in the course of one year after cholecystectomy, QoL improves in all domains of life, except the domain of Social Relationships. Fatigue and trait anxiety have a negative impact on improvements in QoL at one year, whereas the impact of biliary and dyspeptic symptoms on QoL is negligible. QoL should be the starting point for patient centered care in gallstone disease, which implicates preoperative screening for fatigue and high trait anxiety, careful consideration of cholecystectomy, and offering psychological interventions in patients with psychological risk factors.

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Chapter 8

General discussion and clinical implications

This thesis describes the results of a prospective follow-up study investigating recovery of patients with cholelithiasis in the first year after cholecystectomy. We investigated symptomatic outcomes and quality of life (QoL) at postoperative intervals of different lengths. The aim of the study was to identify predictors of negative outcomes after cholecystectomy among clinical and psychosocial variables. In this final chapter, the main findings of this research are discussed and put in the perspective of the implications for clinical practice. Furthermore, methodological considerations and recommendations for future research are presented.

Main findings of the research

Symptomatic outcome

Cholecystectomy is the preferred treatment in symptomatic gallstone disease (cholelithiasis)[1, 2]. Overall, previous outcome research after cholecystectomy lacks distinctness and clarity. Earlier studies presented a variety of outcome measures and described a multitude of predictors of symptomatic outcomes[3-12]. The majority of these studies focussed on postoperative intervals longer than six months. To date no study has investigated outcomes at six weeks after cholecystectomy, even though clinically this is the most relevant interval as greatest recovery takes place in this time-period[13]. Therefore, the aim of the research presented in chapter 2 was to identify predictors of symptomatic outcome six weeks after cholecystectomy. At six weeks, patients with preoperative biliary symptoms had a better chance to be free of symptoms after cholecystectomy than patients reporting dyspeptic symptoms. Nevertheless a quarter of the patients reported persisting biliary symptoms while even half of the patients reported persisting dyspeptic symptoms six weeks after cholecystectomy. These persistence rates are consistent with findings presented in a review on improvement of upper abdominal pain and dyspeptic symptoms after cholecystectomy[14]. This finding suggests that a shift from preoperative biliary to postoperative dyspeptic symptoms, found at longer postoperative intervals[5], could already be observed at six weeks after cholecystectomy. Investigation of risk factors in this study identified preoperative dyspeptic symptoms, more specifically bad taste and flatulence, as risk factors for the report of biliary symptoms at six weeks. In addition, patients with preoperative flatulence had a three to four times greater risk of persistence of biliary and dyspeptic

symptoms. In accordance with findings at later postoperative intervals[5, 6, 10], dyspeptic symptoms seem to be a risk factor for persisting symptoms at six weeks post-cholecystectomy. Stratification of the sample by sex, pointed out that these predictors could only be identified in women.

The scope of predictors was broadened and personality traits were integrated in the design as potential risk factors. So far, the impact of trait anxiety (TA), which is a disposition to respond with heightened anxiety to threatening situations[15], was examined at short postoperative intervals. TA is found to be a predictor of emotional and physical well being and use of analgesics within five days after cholecystectomy[16, 17]. Inconclusive evidence suggests that TA is a predictor of early postoperative pain[16-18]. However, long term impact of TA on post-cholecystectomy outcomes has not been investigated before. Therefore, in chapter 3, the objective was to identify predictors, clinical variables and TA, of negative symptomatic outcome at six weeks. Our study demonstrated a lack of symptomatic improvements in patients with high trait anxiety (HTA), whereas symptoms decreased in patient without this characteristic (NHTA patients). Preoperative clinical symptoms and HTA both predicted the report of postoperative symptoms. Another study also demonstrated that clinical symptoms and personality traits both predicted post-cholecystectomy outcomes[10]. Remarkably, the persistence of biliary symptoms, which is associated with an unsuccessful procedure, is predicted by HTA alone, and not by clinical symptoms. In addition, HTA patients had a seven times greater risk of persistence of biliary symptoms than NHTA patients. Although we established that HTA is an important predictor of post-cholecystectomy outcomes, the mechanism of influence remains unknown. As patients with HTA have higher pain sensitivity and more often suffer from gastrointestinal conditions[19, 20] the report of persistent symptoms may be subjective in nature.

In line with other studies in the field, Chapter 4 focussed on postoperative outcomes at an interval of six months. Typically, persistence rates of biliary and dyspeptic symptoms had not changed compared to the measurement at six weeks (chapter 2 and 3). At six months, preoperative symptoms and HTA both predicted symptomatic outcomes. HTA, the use of psychotropic medication, and non-specific symptoms were risk factors for the report of biliary symptoms, whereas dyspeptic and non-specific symptoms were risk factors for the report of dyspeptic symptoms at six months. Also, the risk of persistence of preoperative biliary symptoms was heightened if patients were characterised by HTA, used psychotropic medication, and reported non-specific symptoms preoperatively.

Furthermore, patients with preoperative non-specific symptoms were also at risk for persistence of dyspeptic symptoms. These results suggest that besides dyspeptic symptoms and HTA, non-specific symptoms are also predictive of negative outcomes after cholecystectomy. The current study suggests that the impact of non-specific symptoms may only be noticeable at longer postoperative intervals, and not yet at six weeks. The findings described in this chapter indicate that non-specific symptoms should be regarded as an independent predictor, and not merely as the consequence of comorbidities or cholelithiasis. To our knowledge, the impact of non-specific symptoms like general malaise, fatigue, weight change, decreased sexual functioning, and other non-specific symptoms, on post-cholecystectomy outcomes has not been investigated before.

Previous studies investigating six months symptomatic outcome used a variety of criteria for inclusion, designs, outcome measures, and moments of follow-up[3, 5, 6, 21]. Therefore, in chapter 5, the aim was to identify predictors of six months symptomatic outcome by a categorisation that was based on disease-specific symptoms and which should be helpful for surgeons and other physicians treating patients with cholelithiasis. To enhance clinical applicability of our results, patients were stratified by preoperative symptom report: biliary symptoms only, dyspeptic symptoms only, and a combination of biliary and dyspeptic symptoms. Patients with preoperative biliary symptoms had the best prognosis, as two thirds of these patients were free of symptoms at six months. In contrast, two thirds of patients having only dyspeptic symptoms reported persistence of these symptoms at six months. Investigation of predictors demonstrated that non-specific symptoms were a risk factor for postoperative symptoms in patients with preoperative biliary or in patients with preoperative dyspeptic symptoms only. Furthermore, patients having only dyspeptic symptoms and patients using psychotropic medication had a five times higher chance at persistence of the preoperative symptom pattern. A differentiation between postoperative outcomes demonstrated that patients with purely dyspeptic symptoms and non-specific symptoms both had a higher chance to report only dyspeptic symptoms at six months. Compared to patients without these characteristics, patients using psychotropic medication and patients with non-specific symptoms had an eight to nine times higher risk at a combination of biliary and dyspeptic symptoms at six months. HTA was the only risk factor for the experience of biliary symptoms only at six months. Compared to NHTA patients, HTA patients had a ten times higher chance to experience biliary symptoms at six months after surgery.

Chapter 6 presented the investigation of one year symptomatic outcome and the identification of predictors of outcome at this postoperative interval. Previous studies established risk factors of post-cholecystectomy outcome and found dyspeptic symptoms, pain characteristics, personality traits, and psychological symptoms to be risk factors of negative outcome at one year[8, 10]. Although two other studies indicated that symptomatic outcome at one year could not be predicted[9, 22], we found that preoperative symptomatology was decisive for postoperative outcomes. At one year, patients suffering from preoperative biliary symptoms only had best convalescence as they reported to be free of symptoms most often. This finding is in line with another study indicating that patients with typical biliary symptoms have best convalescence after a postoperative interval of ten years[12]. Furthermore, patients with non-specific symptoms had a three times greater chance of biliary and dyspeptic symptoms at one year after cholecystectomy. The findings described in this chapter indicate that the presence of non-specific symptoms is a valuable predictor for longer postoperative intervals (> 6 months). In contrast, HTA was not found to be a predictor for symptomatic outcome at one year and could merely be considered as a predictor of symptomatic outcome within six months after cholecystectomy.

In Chapter 7, the process of symptomatic improvement during the first year following cholecystectomy was investigated. Symptomatic improvement only took place within the first six weeks after cholecystectomy and not later during postoperative recovery, which is in line with clinical experience[13].

Taken together, the results of our study indicate that symptomatic recovery mainly takes place within 6 weeks after cholecystectomy. Patients reporting only biliary symptoms showed complete symptomatic relief most often, whereas patients with only dyspeptic symptoms showed persistence of symptoms most frequently. The preoperative symptomatology of cholelithiasis may be a valuable criterion for outcome after cholecystectomy, as preoperative dyspeptic symptoms were found to be strongly associated with negative symptomatic outcome. In addition, other characteristics also appeared to be valuable for the prognosis of symptomatic outcome. Within the first six months after cholecystectomy, HTA was a risk factor for persistent biliary symptoms. However, these preliminary findings suggest that the impact of HTA is mainly noticeable within six months after cholecystectomy, whereas HTA had no statistically significant influence on symptomatic recovery at one year. Furthermore, preoperative non-specific symptoms were a valuable predictor of negative symptomatic outcome at an interval of

six months or longer after cholecystectomy. Finally, the use of psychotropic medication may be a predictor of long term symptomatic outcome, although evidence of this work is indecisive.

Quality of life

The concept quality of life (QoL) has become widely accepted as an outcome measure for medical procedures and treatment. QoL is a broad ranging concept integrating the individual patient's overall functioning (reaching beyond the scope of physical, psychological, and social functioning), and the evaluation of that functioning. In chapter 6, we investigated overall QoL and general health at one year post-cholecystectomy and found that patients with dyspeptic symptoms demonstrated no improvement in QoL, whereas patients with biliary symptoms or with a combination of biliary and dyspeptic symptoms did. Furthermore, preoperative symptom classification (based on biliary, dyspeptic, or biliary and dyspeptic symptoms), abdominal comorbidity and HTA were risk factors for lower QoL at one year.

Within the field of cholecystectomy, several studies have focussed on the subjective experience of patients investigating health status and patients' satisfaction[5, 11, 23-30]. However, there is a paucity of studies that measure the patients' evaluation of life after a cholecystectomy. Improvements in QoL and the identification of predictors among clinical and psychosocial variables, were further addressed in chapter 7. With the exception of the dimension Social Relationships, multiple dimensions of QoL improved in the course of one year. Typically, improvements of QoL, biliary and dyspeptic symptoms, depressive symptoms, and anxiety all took place within the first six weeks after cholecystectomy. TA had a negative impact on all QoL domains, except Physical Health. Fatigue had a negative effect on QoL in the domain Physical Health and overall QoL and general health. With regard to one year improvement of QoL in the domain Physical health, fatigue and TA had a negative effect, whereas depressive symptoms and flatulence had a positive effect. General malaise and other non-specific symptoms had a negative impact on QoL in the domains Social Relationships and Environment, respectively. Furthermore, TA had a negative effect on improvements in overall QoL and general health, whereas depressive symptoms had a positive effect on improvements in overall QoL and general health. As depressive symptoms can be reactive to situations or conditions, long lasting symptoms and pain and the prospective of hospital admission and surgery may worsen depressive symptoms preoperatively. As depressive symptoms

are related to QoL[31-33], relief of depressive symptoms may have an additional effect on improvements QoL. Although TA is no predictor of symptomatic outcome (chapter 6), it is a predictor of QoL and improvements of QoL at one year after cholecystectomy. This finding emphasizes the difference between QoL and more objective measures such as symptom report, even if these measures are based on self reports. With regard to fatigue, to our knowledge no other prospective studies have investigated the impact of fatigue on post-cholecystectomy outcomes.

In summary, improvements in QoL took place within the first six weeks after cholecystectomy. Psychosocial variables, namely TA and depressive symptoms, had an impact on improvements in QoL in the course of one year. Fatigue also had an impact on QoL, but only on improvements within the domain Physical health.

Methodological considerations

Drawbacks

The work presented in this thesis has several drawbacks. First of all, data collection took place within a single hospital, which may limit the generalisability of the results to the entire population of patients. Secondly, the use of a self-constructed symptom checklist may limit the comparability with results of other studies. We found that the majority of studies in the field used self-constructed checklists and to our knowledge no cholelithiasis-specific symptom checklist has been developed yet. Incidentally, some studies used standardised gastrointestinal questionnaires to list cholelithiasis-specific symptoms. However, we believe that checklist for gastrointestinal symptoms measure more than only cholelithiasis-specific symptoms and therefore may be inappropriate for this purpose. As the checklist used in the current work was based on the experience of patients in focus groups, clinical experience of surgeons, and checklists used in other studies, we believe that our checklist may be an appropriate solution. Thirdly, for practical reasons, e.g. to enhance the applicability of our results in clinical practice, we categorised biliary and dyspeptic symptoms in congruence with other studies[5, 34]. The categorisation used in this work may be disputable, as nausea and upper abdominal pain could also be components of a dyspeptic pattern[35]. However, as the clinical symptoms of cholelithiasis are ambiguous and biliary colic may be the only discerning symptom[1], the use of individual symptoms may be preferred. Dependent on the aim of the study, choice of individual symptoms or categories should be motivated. Fourthly, in chapters 2

to 6, a single follow-up measurement was used to investigate symptomatic improvement. Consequently it remains unclear whether symptoms actually persisted, or disappeared and emerged at some time after cholecystectomy. The use of multiple measurements, or different questioning, should clarify this matter. Fifthly, in the current design we did not control for confounding variables. Especially at longer postoperative intervals (chapter 5, 6, and 7) outcomes may be confounded by changes in comorbidity or special life events. We acknowledge that we are unable to pronounce upon the pure effect of cholecystectomy, but we believe that this appropriately mimics the real-life situation of clinical practice where postoperative wellbeing has to be predicted based on preoperative characteristics alone. Finally, response rates may be negatively influenced by the number of follow-ups in our designs. Besides the preoperative measurement, patients had to complete questionnaires at 10 days, 6 weeks, 6 months, and 1 year after cholecystectomy. We believe that especially in the early stage participation might be demanding for patients, which may result in a high number of non-responders and drop-outs. After examination it was clear participants, non-responders and drop-outs did not differ on demographic and clinical variables.

Strengths

The present work has several improvements over other studies in the field. First of all, the study investigated a substantial cohort of consecutive patients. As approximately 95% of the patients agreed to participate, the results of the study could be easily generalised to the average patient with symptomatic cholelithiasis. Furthermore, criteria for in- and exclusion were clear-cut and guaranteed a homogeneous group of patients with symptomatic cholelithiasis, undergoing a laparoscopic cholecystectomy. Confounders such as different operative techniques, emergency procedures, previous abdominal surgery, worse physical condition (ASA class III and IV), and psychiatric disease, which all may have an impact on postoperative outcome were excluded from the design. By contrast, former studies assessed heterogeneous or undifferentiated samples[3, 11, 22, 23]. The current work has a unique contribution to clinical research in cholecystectomy, as it is the first study that addresses improvements in QoL (chapter 6 and 7), uses non-specific symptoms as predictor, and is the first to assess six weeks recovery. Furthermore, the present work investigated QoL and broad psychosocial variables at multiple intervals (chapter 7), and considered post-cholecystectomy recovery as a dynamic process instead of a static inventory.

Implications for future research

Several chapters of this thesis described postoperative recovery at six weeks after cholecystectomy (Chapter 1, 3, and 7), which appeared to be a critical interval for post-cholecystectomy recovery. Clinical experience teaches that greatest recovery takes place within six weeks. Future research should investigate the process of improvement within the first weeks after cholecystectomy and identify the critical period for recovery. Chapter 2 demonstrated that predictors of negative outcome may be different in men and women. As the sample of men was small, sex differences were not elaborated upon in other chapters. As men and women differ with regard to preoperative presentation of cholelithiasis and postoperative recovery[36], this preliminary finding should be corroborated in future studies based on larger samples. So far, our work highlighted preoperative characteristics and symptoms that have not been investigated with respect to post-cholecystectomy outcomes. The impact of preoperative non-specific symptoms and fatigue needs to be addressed further in future studies. Moreover, research in personality traits predicting post-cholecystectomy outcome has been limited and only few studies reported the effects of neuroticism, introversion, and trait anxiety. We suggest that investigating the impact of other personality traits on post-cholecystectomy recovery should be subject of future studies. Most important, the findings presented in this thesis provide evidence that post-cholecystectomy recovery is a multidimensional process containing both physical and psychological aspects. Future comprehensive research should investigate the mechanisms through which these physical and psychological aspects influence symptomatic recovery and QoL.

Clinical implications

Risk assessment in cholecystectomy is of interest to surgeons involved in the decision process for cholecystectomy, but even more so to internists, gastroenterologists and general practitioners who see patients with broad gastrointestinal symptoms and who may refer patients with a suspicion of cholelithiasis for surgical consultation. These professionals have to deal with the heterogeneous symptomatology of cholelithiasis and the ongoing uncertainty whether preoperative gastrointestinal symptoms are related to demonstrated gallstones or not. Relief of gastrointestinal symptoms and pain after cholecystectomy provides the ultimate proof that symptoms and gallstones were indeed

related. As preoperatively diagnostic criteria give little support for consideration about cholecystectomy, the results presented in this thesis may hand physicians alternative tools to improve clinical decision in cholelithiasis.

Results presented in this thesis principally show that the consideration for performing cholecystectomy should be made from a holistic perspective. As both physical and psychological aspects have an impact on outcome after cholecystectomy, physicians should realise that insight into patients' psychological characteristics has an additional value for their own medical practice. Collecting information about psychological characteristics and non specific symptoms, e.g. trait anxiety, depressive symptoms, fatigue, general malaise, weight-change, decreased sexual functioning, and other non-specific symptoms, deserves special attention during anamnesis in selected patients. A short psychological screening, consisting of checklists such as the STAI, CES-D, and FAS, may have an additional value in the identification of patients at risk for negative outcomes after cholecystectomy. Furthermore, information on expected postoperative outcomes should be tailored to the patient's individual risks in order to create realistic expectations of postoperative recovery. As cholecystectomy is an elective procedure, which is ideally performed and planned in dialogue with the patient, sharing of realistic prognostic information may facilitate the joint decision process by patient and surgeon.

The ability to recognise patients at risk for negative postoperative outcomes may have implications for the management of cholelithiasis. As elective cholecystectomy is in fact a prophylactic treatment[37], positive outcomes such as improvement of QoL and prevention of complications may be the incentive to operate. However, surgeons and other physicians also should be imbued with the fact that only half of the patients are free of symptoms after cholecystectomy. Therefore, 'wait and see' management should be considered as an alternative, especially in patients with a high risk profile for negative outcomes. Actually, the risk of postoperative complications, such as cholecystitis, acute pancreatitis, or biliary duct obstruction is quite small (1% – 2% yearly)[38, 39]. Biliary pain only recurs in one third of the patients with previous biliary attacks longer than one year before. Also, it is often neglected that cholecystectomy still entails the risk of mortality (0.2% – 0.3%)[40, 41], and local and systemic complications (3.5% and 2.7%, respectively)[40]. Therefore, in patients with a heightened risk for negative postoperative outcomes conservative treatment may be preferred over cholecystectomy. Furthermore, general practitioners and gastroenterologists may feel the necessity to refer patients for surgical consultations immediately. As wait and see entails only a small risk of negative

consequences, it may be a good alternative, especially in patients with dyspeptic symptoms only, HTA, and non-specific symptoms, who show limited symptomatic improvements after cholecystectomy.

Current clinical guidelines indicate cholecystectomy as the treatment of choice in symptomatic cholelithiasis, despite the fact that many patients report persistent symptoms. These guidelines focus on symptomatic outcomes and are primarily developed from a surgical point of view[1]. As physicians generally underestimate the number of symptoms and pain experienced by patients[42], classical endpoints may inadequately represent patients' experience. Therefore, subjective outcome measures should be incorporated in future guidelines. Further, the risk factors described in this thesis may be elaborated in the indication of cholecystectomy. In patients with dyspeptic symptoms only, HTA and non specific symptoms, tightening of the indication is advisable. A patient-tailored approach, in which cholecystectomy is considered the golden standard for patients with biliary symptoms only, but as a treatment option in patients with dyspeptic symptoms, HTA and non-specific symptoms, should be preferred. We recommend that future guidelines also integrate characteristics from a broad perspective.

We advocate a multidisciplinary management of cholelithiasis in high risk patients. Psychological expertise may not only be valuable in screening for high risk patients, but also in the treatment of patients to minimise the negative effect of HTA on postoperative recovery. As HTA is a stable personal trait, changing this characteristic will be a laborious process that may overshoot the mark. We believe that interventions aimed at dealing with anxiety provoking and otherwise threatening situations, such as the expansion of coping strategies, should be the focus of psychological counselling. From the perspective of cognitive behavioural therapy[43-45], negative and unrealistic thoughts make a situation more or less threatening to the individual. The identification and challenge of negative automatic thoughts and attributions may neutralise negative feelings and may consequently affect the patient's behaviour and reaction to postoperative gastrointestinal symptoms. This approach has achieved successes in the treatment of patients with functional dyspepsia and other gastrointestinal symptoms[46, 47]. Mindfulness based stress reduction (MBSR)[48] or mindfulness based cognitive therapy (MBCT)[49], which are successfully applied in patients with chronic pain and stress[50, 51], may help some HTA patients to accept their symptoms and avoid rumination, which may be anxiety provoking itself. As HTA patients are more sensitive to gastrointestinal

symptoms and pain[19, 20], and report higher activation of the sympathetic nervous system[52], this approach may reduce the negative impact of HTA. Preoperative interventions may diminish negative postoperative outcomes in these patients. Besides, psychological counselling may be supportive in case of conservative management and may help specific patients dealing with persistent symptoms after surgery. Clinical intervention studies should investigate the postoperative benefits of psychological interventions.

The implications identified above hold the promise that the number of unnecessary cholecystectomies may be reduced. A turn should be made towards an approach with the patient's subjective needs and expectations as core elements. Gaining a broad perception of the patient's symptoms and characteristics and providing patient-specific information on postoperative risks will be two essential steps in the process of change. Secondly, the decision process for surgical intervention or alternative treatments will lead to further innovation in the management of cholelithiasis. We believe that going beyond the borders of individual professional fields will provide new insights that may ultimately pave the way for optimized treatment approaches in cholelithiasis. Finally, selective performance of cholecystectomy and preservation of the procedure to patients with a good chance of positive outcomes will result in greater cost effectiveness in health care.

Concluding remarks

The research presented in this thesis suggests there is potential for further improvements in the treatment of cholelithiasis. Clinical decision making in cholelithiasis could be better tuned to the individual patient by using a more comprehensive approach, integrating both physical and psychological aspects. Patients reporting only biliary symptoms show best symptomatic improvement and are most often free of symptoms after cholecystectomy. Preoperative dyspeptic symptoms, trait anxiety, and non-specific symptoms (e.g. fatigue) are identified as risk factors for negative symptomatic improvements. In addition, trait anxiety and non-specific symptoms are predictors for improvements in QoL. On the contrary, preoperative biliary and dyspeptic symptoms do not have an impact on QoL at one year after cholecystectomy.

Insights in psychological risk factors, may lead to alternative decision criteria, differentiation of treatment approaches, and tightening of the indication for

cholecystectomy. Besides cholecystectomy, conservative treatment may be considered as a viable alternative for high risk patients. Psychological counselling may have an additional value for selected patients with a high risk of negative outcomes. We believe that a multidisciplinary approach, going beyond the borders of individual professional fields, will ultimately lead to differentiated treatment options tailored to individual patients' needs.

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Chapter 9

Samenvatting

Galsteenlijden, diagnostiek en behandeling

Galsteenlijden (cholelithiasis) komt veel voor. In Westerse landen lijdt 5 – 22% van de bevolking aan deze aandoening en alleen in Nederland wordt jaarlijks bij 30.000 mensen cholelithiasis gediagnosticeerd[1-4]. Naast hoge leeftijd en vrouwelijk geslacht, zijn hoge Body Mass Index (BMI), de invloed van oestrogeen, etniciteit, roken, alcohol gebruik en gebruik van cholesterolverlagende medicatie van invloed op het ontstaan van galstenen[5]. De meeste mensen met galstenen blijven klachtenvrij[1] en slechts 10 – 30% rapporteert klinisch significante symptomen, waarbij men spreekt van symptomatisch galsteenlijden[6-12]. Galsteenkolieken, die gedefinieerd worden als 'een hevige, aanhoudende pijn, die 15 – 30 minuten duurt, meestal gelokaliseerd is in de (rechter) bovenbuik en soms uitstraalt naar de rug', vormen bij symptomatisch galsteenlijden het meest onderscheidende symptoom[13]. Deze galsteenkolieken gaan vaak gepaard met misselijkheid en braken[14]. Overige gastrointestinale klachten, die men veelal aanduidt met de term dyspeptische klachten, komen bij symptomatisch galsteenlijden eveneens veelvuldig voor. Op basis van klinische symptomen alleen is het moeilijk om bij deze aandoening een correcte diagnose te stellen. Aanvullend echografisch onderzoek naar de aanwezigheid van galstenen wordt geadviseerd[15].

Het operatief verwijderen van de galblaas (cholecystectomie) is de gouden standaard bij symptomatisch galsteenlijden. Na een cholecystectomie rapporteert ongeveer één derde van alle patiënten persistentie van klachten[16-21]. De risico's bij een cholecystectomie worden onderschat, maar zijn zeker aanwezig. Het gaat daarbij om het risico op postoperatieve complicaties (5.0%), galwegletsel (0.2% – 1.0%) en overlijden (0% – 0.2%)[22, 23]. Een conservatief beleid lijkt veilig, aangezien slechts 31% van de patiënten binnen één jaar opnieuw een aanval van galsteenkolieken krijgt[24] en de kans op het optreden van complicaties, zoals acute cholecystitis, acute pancreatitis en galwegobstructie, gering is (jaarlijks 1% – 2%)[25, 26]. Patiënten die een cholecystectomie dan wel een conservatieve behandeling ondergaan, lijken vijf jaar na de diagnose niet te verschillen ten aanzien van kwaliteit van leven en ervaren pijn[27].

Samenvatting van de belangrijkste resultaten

In deze dissertatie wordt een prospectief follow-up onderzoek beschreven dat zich richt op het identificeren van predictoren voor symptomatische uitkomsten en kwaliteit van

leven zes weken, zes maanden en één jaar na cholecystectomie. Patiënten met symptomatisch galsteenlijden en een indicatie voor een electieve cholecystectomie werden benaderd voor deelname aan het onderzoek. Voor de operatie vulden patiënten een set vragenlijsten in, die bestond uit een symptomen checklist en vragenlijsten over ervaren pijn (VAS), situationele en dispositionele angst (STAI state en trait), depressieve gevoelens (CES-D), vermoeidheid (FAS) en ervaren kwaliteit van leven (WHOQOL-BREF). Tien dagen, zes weken, zes maanden en één jaar na de operatie ontvingen patiënten opnieuw dezelfde vragenlijsten per post. Cholecystectomie werd uitgevoerd volgens een standaard chirurgische procedure en onder een standaard anaesthetisch regime.

Symptomatische uitkomsten

In onderzoek naar uitkomsten van cholecystectomie richt het merendeel van de studies zich op een postoperatieve periode langer dan 6 maanden en 'klassieke' uitkomstmaten, zoals complicaties en symptomen. Na cholecystectomie lijken typisch biliaire symptomen te verbeteren, terwijl dyspeptisch symptomen vaker aanhouden. Ongeveer één derde van de patiënten rapporteert persistentie van symptomen en pijn, waarbij met name flatulentie en diarree postoperatief vaak voorkomen. Voorgaand onderzoek toonde aan dat slechte resultaten na cholecystectomie samenhangen met preoperatieve dyspeptische klachten, het ervaren van pijn *en* symptomen, het gebruik van psychofarmaca en psychologische factoren, zoals bepaalde persoonlijkheidstrekken. Na een korte inleiding en uiteenzetting van de onderzoeksopzet (hoofdstuk 1), beschrijft hoofdstuk 2 de resultaten zes weken na cholecystectomie. Na zes weken rapporteerden respectievelijk een kwart en de helft van de patiënten persistentie van biliaire en dyspeptische klachten. Preoperatieve dyspeptische symptomen, met name flatulentie en een vieze smaak in de mond, waren risicofactoren voor aanhoudende symptomen zes weken na cholecystectomie. Bovendien bleken risicofactoren alleen bij vrouwelijke patiënten aantoonbaar en niet bij mannen.

In hoofdstuk 3 wordt aangetoond dat naast klinische factoren, ook persoonlijkheidstrekken van invloed zijn op het postoperatief herstel. Op het gebied van persoonlijkheid is gekeken naar patiënten met een hoge dispositionele angst. Deze patiënten hebben een sterke neiging om met verhoogde angst te reageren op bedreigende situaties. Zes weken na een cholecystectomie rapporteerden patiënten met een hoge dispositionele angst geen verbetering van symptomen, in tegenstelling tot patiënten zonder een hoge dispositionele angst. Naast klinische factoren blijkt hoge

dispositionele angst een belangrijke risicofactor voor persistentie van symptomen zes weken na de operatie. Hoofdstuk 4 beschrijft het onderzoek naar aanhoudende biliaire en dyspeptische klachten zes maanden na cholecystectomie. Patiënten met hoge dispositionele angst, niet-specifieke klachten (zoals algehele malaise en vermoeidheid) en patiënten die psychofarmaca gebruikten hadden een groter risico op persistentie van biliaire symptomen zes maanden na cholecystectomie. Bovendien hadden patiënten met niet-specifieke symptomen een verhoogd risico op persistentie van dyspeptische symptomen.

In hoofdstuk 5 worden patiënten op basis van preoperatieve symptomen ingedeeld in verschillende groepen (alleen biliaire symptomen, alleen dyspeptische symptomen, een combinatie van biliaire *en* dyspeptische symptomen). Zes maanden na cholecystectomie waren vooral patiënten met alleen biliaire symptomen symptoomvrij. Patiënten met alleen dyspeptische symptomen rapporteerden vooral persistentie van symptomen.

Over het geheel genomen, hadden patiënten met niet-specifieke symptomen een verhoogde kans op biliaire en/of dyspeptisch symptomen zes maanden na cholecystectomie. In vergelijking met patiënten zonder hoge dispositionele angst, hadden patiënten *met* hoge dispositionele angst hadden een tien maal zo grote kans op postoperatieve biliaire symptomen. In hoofdstuk 6 en 7 volgt onderzoek naar de resultaten één jaar na cholecystectomie. Na één jaar waren patiënten met alleen biliaire symptomen het meest vaak vrij van symptomen. Patiënten met niet-specifieke symptomen hadden een drie maal zo grote kans op biliaire en/of dyspeptische symptomen na één jaar, dan patiënten *zonder* niet-specifieke symptomen. In hoofdstuk 7 wordt beschreven dat symptomatische verbetering alleen plaatsvindt in de eerste zes weken na cholecystectomie.

Kwaliteit van leven

De laatste jaren zien we bij de evaluatie van chirurgische procedures een toenemende belangstelling voor de subjectieve ervaring van de patiënt. Kwaliteit van leven (KvL) is een subjectieve uitkomstmaat die niet alleen aangeeft hoezeer een patiënt beperkt is in zijn/haar fysiek, psychisch en sociaal functioneren. KvL omvat het functioneren in brede zin en de wijze waarop de individuele patiënt zijn/haar niveau van functioneren zélf ervaart.

In hoofdstuk 6 werd algehele KvL en gezondheid voor de verschillende groepen patiënten in kaart gebracht. Patiënten met alleen dyspeptische symptomen ervoeren

geen verbetering in algehele KvL en gezondheid in het eerste jaar na cholecystectomie, in tegenstelling tot patiënten met alleen biliaire symptomen of biliaire *en* dyspeptische symptomen. Preoperatieve symptomen (dyspeptisch, biliair, of dyspeptisch *en* biliair), hoge dispositionele angst en comorbide abdominale aandoeningen hadden een effect op algehele KvL en gezondheid na één jaar. Hoofdstuk 7 beschrijft verbeteringen in verschillende domeinen van KvL. In het eerste jaar na cholecystectomie vonden verbeteringen in KvL, depressieve symptomen en angst alleen plaats gedurende de eerste zes weken. Vermoeidheid verbeterde niet in het eerste jaar na cholecystectomie. Dispositionele angst had een negatief effect, terwijl preoperatieve depressieve symptomen een positief effect hadden op KvL één jaar na cholecystectomie. Preoperatieve vermoeidheid had alleen een effect op de fysieke aspecten van KvL.

Afsluitende opmerkingen en conclusies

Concluderend kan worden vastgesteld dat op lange termijn de helft van alle patiënten niet symptoomvrij is na een cholecystectomie. Het vroegtijdig herkennen van patiënten met een verhoogd risico op negatieve resultaten na cholecystectomie is van belang om tot de keuze voor een optimale behandeling te komen. Patiënten met zuiver biliaire symptomen hebben de grootste kans om helemaal van hun klachten af te komen. Met name patiënten met zuiver dyspeptische symptomen lopen het risico dat de klachten blijven voortbestaan na cholecystectomie. Naast ziektespecifieke symptomen, hebben psychosociale factoren en niet-specifieke symptomen een effect op het symptomatisch beloop en KvL na een cholecystectomie. Hoge dispositionele angst en niet-specifieke symptomen zijn risicofactoren voor negatieve symptomatische uitkomsten na cholecystectomie. Dispositionele angst en preoperatieve vermoeidheid hebben beide een negatief effect op verbeteringen in KvL één jaar na cholecystectomie, terwijl preoperatieve biliaire en dyspeptische symptomen geen effect hebben. Aanvullend onderzoek is noodzakelijk om andere psychosociale variabelen als voorspellers van negatieve uitkomsten te identificeren.

Dit proefschrift onderschrijft het belang van een multidisciplinaire diagnostiek en behandeling van patiënten met een verdenking op symptomatisch galsteenlijden. Psychologische en fysieke patiëntkenmerken moeten geïntegreerd worden om op basis van het totaalbeeld tot een optimaal behandeladvies te komen voor de individuele patiënt. Aangezien een conservatieve behandeling van galsteenlijden veiliger is dan over

het algemeen wordt verondersteld, dient men bij patiënten met een hoog risico op negatieve postoperatieve uitkomsten zeker de afweging te maken tussen cholecystectomie en een expectatief beleid.

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Marlies Mertens, Oktober 2009

About the author

Marlies Mertens was born on October 4th 1972, in Bergen op Zoom, the Netherlands. She completed her pre-university education at the Mollerlyceum in Bergen op Zoom. From 1991 to 1998, she studied Teaching and Performing Arts at the Fontys Conservatory in Tilburg, the Netherlands. After her graduation she worked as a musician and music teacher until 2006. From 2001 to 2006, she studied Clinical Health Psychology at Tilburg University. She completed clinical and research internships at the Leiden University Medical Centre and the Twee Steden Hospital in Tilburg, respectively. From 2005 to 2007, she worked as a psychologist with physically disabled adults at Gemini Zorg en Dienstverlening in Tilburg. From 2007 till present, she has worked as a psychologist in nursing homes and day care centres at De Zorgboog in Bakel. In 2005 she started her PhD project at Tilburg University, investigating predictors of recovery after cholecystectomy. In January 2010, she will start the post-graduate training for Health Psychologist at the Maastricht University Medical Centre.

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